Gynecologic Oncology 148 (2018) 239–246

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

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.

ARTICLE INFO

Article history:
Received 29 October 2017
Received in revised form 4 December 2017
Accepted 5 December 2017
Available online 13 December 2017

Keywords:
Gestational trophoblastic neoplasia
Choriocarcinoma
Human chorionic gonadotropin
Chemotherapy

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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https://doi.org/10.1016/j.ygyno.2017.12.007

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.

2.3. Initial management of patients with choriocarcinoma

After being referred to one of BRCGTD, each patient's clinical history was obtained and physical examination was performed. Patients were questioned about the antecedent gestations to determine which pregnancy gave rise to the tumor. On the first visit, an initial hCG level was obtained, hormonal contraception was initiated, transvaginal Doppler ultrasound, chest computed tomography and brain, abdomen and pelvis nuclear magnetic resonance imaging were performed.

Measurement of hCG in all thirteen Reference Centers employed the Siemens Diagnostic Products Corporation (DPC) Immulite® assay. The reference value for normal results was an hCG value below 5 IU/L.

If the patient presented with metastatic disease, treatment and follow-up was done according to FIGO 2000 recommendations [9]. However, if the patient had no evidence of metastasis at presentation, she was counseled about immediately initiating chemotherapy, according to FIGO 2000 [9], or waiting for at least two weeks to evaluate the hCG trends and disease behavior. If hCG levels increased in two consecutive weeks or plateaued for three weeks in patients that chose expectant management, chemotherapy was initiated [9]. Those noted to have falling hCG levels were rigorously followed with weekly levels of hCG and monthly chest radiograph and Doppler ultrasound scan of the abdomen and pelvis in order to detect early metastasis. After hCG normalization, patients were monitored monthly with hCG levels for 12 months, when they were discharged from the follow-up.

Patients with normal hCG levels, that desired to be treated with chemotherapy, received 3 cycles of consolidation chemotherapy with a single agent. After chemotherapy, all patients were followed for at least one year with monthly hCG surveillance after the first normal hCG value was obtained. When patients did not attend the scheduled visits, a social worker and hospital psychologist actively tried to contact them by phone and telegram to identify what was hindering compliance and to motivate them to return to follow-up.

2.4. Staging, risk factors and treatment of gestational choriocarcinoma

As GCC is a form of GTN, patients were staged according to the FIGO 2000 GTN anatomical staging and assigned a prognostic score for resistance to chemotherapy following the FIGO/WHO Prognostic Scoring System [9]. Lung metastases were detected using a chest X-ray, although computed tomography scans were used in some cases as an aid in follow-up and treatment [9]. Nuclear magnetic resonance imaging of the brain and abdomen was used for patients with visible pulmonary or genital metastasis.

Methotrexate and folinic acid rescue (MTX/FA) 1 mg/kg intramuscular and 0.1 mg/kg per oral, respectively, were used as first line treatment in cases of low-risk GTN. In a few cases there was a contraindication to the use of MTX/FA (due to hypersensitivity or large theca lutein cysts), so treatment with Actinomycin D was initiated. In cases of MTX resistance, second-line chemotherapy was performed with Actinomycin D (Act-D) 1.25 mg/m^2 (max 2.0 mg) IV pulse every 2 weeks or the EMA/CO regimen (etoposide, MTX/FA, Act-D, cyclophosphamide, and vincristine).

2.5. Outcomes

The primary outcome in the expectantly managed group was the need for chemotherapy according to the following criteria: increase in hCG levels over two consecutive weeks or the plateauing of hCG for three weeks. Secondary outcomes included the need of hysterectomy, occurrence of metastasis, the presence of high-risk FIGO score, need of multi-agent chemotherapy, time to remission, relapse or death.

2.6. Variables

The variables that were analyzed included: patient's age (years), gravidity, parity, antecedent pregnancy, clinical presentation at diagnosis of choriocarcinoma, hCG levels at choriocarcinoma diagnosis (IU/L), time between the end of index pregnancy and the initial clinical evaluation at BRCGTD (weeks) and whether chemotherapy was initiated. For patients treated with chemotherapy, the following variables were included: time between uterine evacuation and beginning of chemotherapy (months), WHO/FIGO prognostic risk score, lines of chemotherapy and the number of cycles needed to achieve remission, development of metastasis, time to hCG normalization, duration of follow up (months), relapse or death.

2.7. Statistical analysis

Descriptive analyses of the population were presented as a percentage distribution of the categories when the variables were categorical. In relation to the qualitative variables, the percentage differences were evaluated using the Chi-square statistic, or Fisher's Exact Test as appropriate. For continuous variables, the Shapiro-Wilk test was used to verify the normality of the distribution. The differences of means were evaluated with a Student's *t*-test for variables with normal distributions and non-parametric Mann-Whitney *U* test when data were not normally distributed. The crude odds ratio (cOR) and adjusted odds ratio (aOR) with 95% confidence intervals (95% CI) for needing chemotherapy to achieve remission among Brazilian women with nonmetastatic gestational choriocarcinoma followed initially with expectant management were calculated using a logistic regression model for outcomes with binomial distribution. Variables with statistical significance at $p < 0.05$ were maintained in the adjusted model. The fit of the model was evaluated by the Akaike criterion and Wald test for logistic regression. All statistical analyzes were carried out using the R statistical package.

3. Results

A flow diagram describing the study population appears in Fig. 1. From January 2000 to December 2016, 3191 patients were diagnosed with GTN. Among all patients with GTN, 231 (7.2%) had pathological diagnosis of choriocarcinoma and 199 were nonmetastatic choriocarcinoma (86.1% of all choriocarcinomas). Chemotherapy was initiated immediately in 152 (76.4%) patients per FIGO 2000 guideline, while 47 (23.6%) chose expectant management after being properly counseled and consenting to this option.

Table 1 summarizes the characteristics of Brazilian women with nonmetastatic GCC immediately treated with chemotherapy per FIGO 2000 guidelines or followed with expectant management. Both groups presented with similar characteristics. There was no difference when comparing age (median: 30 versus 28 years, $p = 0.79$), gravidity (median: 2 versus 2 gestations, $p = 0.92$), parity (median: 1 versus 1 delivery, $p = 0.89$), antecedent pregnancy (molar pregnancy: 44.7% versus 46.8%, $p = 0.88$), clinical presentation, hCG at diagnosis of GCC (median 55,678 versus 68,399 IU/L/, $p = 0.13$), time between the end of index pregnancy and arrival at the BRCGTD (median 6 versus 7 weeks, $p = 0.75$) and percentage of patients with normal hCG on arrival at the BRCGTD (20.4 versus 25.5, $p = 0.39$).

Treatment and outcomes of Brazilian women with nonmetastatic GCC is presented in Table 2. Compared to the 100% of women (152 patients) in the immediate treatment cohort who received chemotherapy, only 44.7% (21 of 47 patients) who were expectantly managed needed to receive chemotherapy ($p < 0.01$). There was no difference between the groups regarding the first-line agent of choice (MTX/FA 88.2% versus 85.7%, $p = 0.89$), second-line drug (Act-D 62.5% versus 50%, $p = 0.78$ or

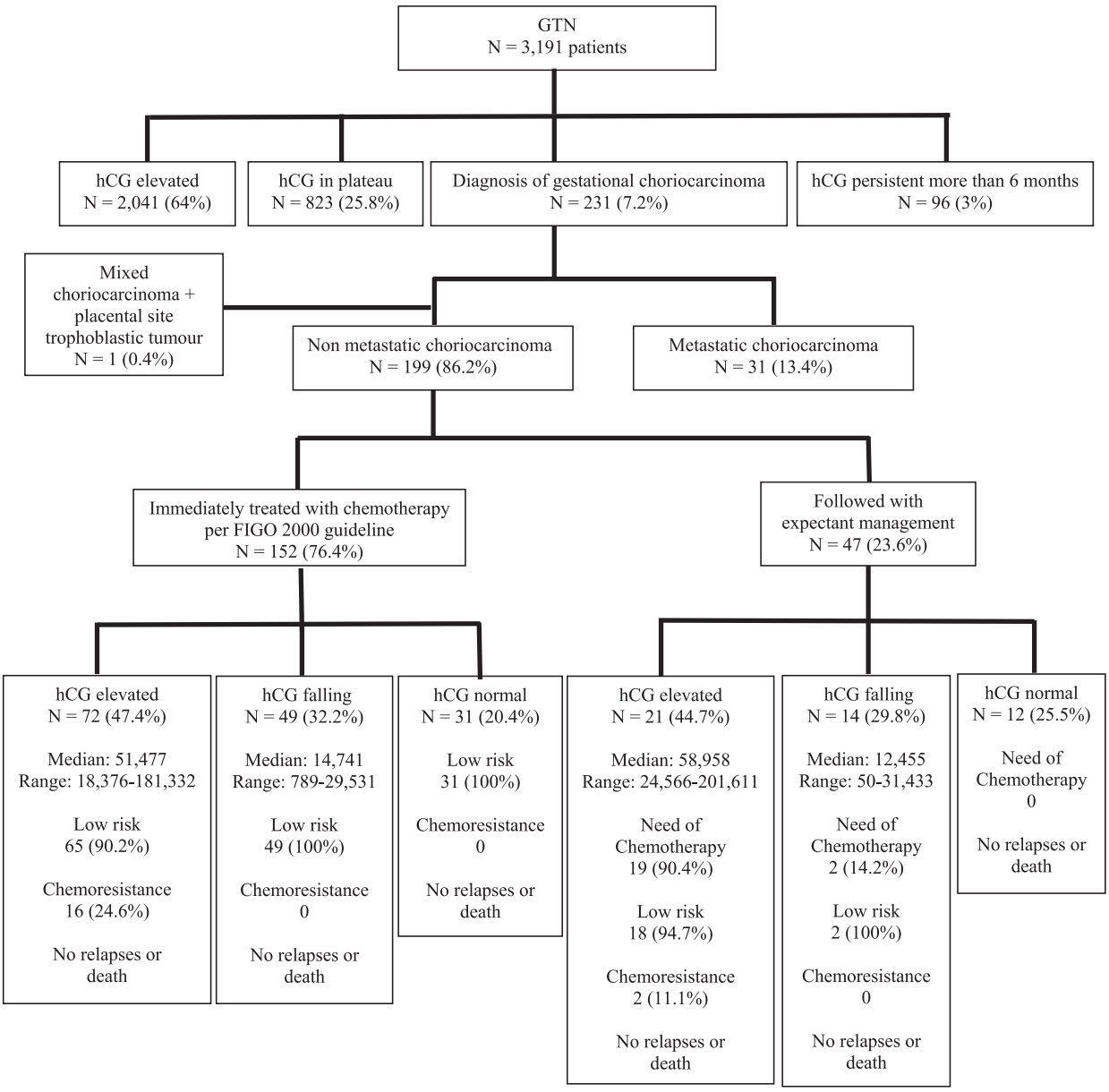

Fig. 1. Flow diagram summarizing the derivation of the study population.

EMA/CO 37.5% versus 50%, $p = 0.09$) or the number of cycles needed to achieve remission. It is striking that 7.9% of the patients immediately treated with chemotherapy per FIGO 2000 guidelines underwent adjuvant hysterectomy before being referred to the participating centers of this study, while no patient in the expectant management group had a hysterectomy ($p < 0.01$).

Table 3 compares the outcomes of Brazilian women with nonmetastatic GCC treated with chemotherapy, either per FIGO 2000 criteria (start chemotherapy immediately after histologic diagnosis of choriocarcinoma) or later due to plateau or elevation of hCG levels after initial expectant management. Even though the time between the last pregnancy and the initiation of chemotherapy was longer in the initial expectantly managed group (median 7 versus 10 weeks, $p = 0.02$), this did not increase the WHO/FIGO prognostic risk score (median 4 versus 4, $p = 0.73$), the rate of high risk GTN (4.6% versus 4.7%, $p = 0.89$), need for multi-agent regimens (8.5% versus 4.7%, $p = 0.14$) or the number of chemotherapy cycles to achieve remission (median 6 versus 6 cycles, $p = 0.91$). Similarly, there was no difference in rate of chemoresistance (10.5% versus 9.5%, $p = 0.94$) and metastatic disease (4.6% versus 4.7%, $p = 0.87$). Although patients with initial expectant management required a longer follow up time (median 14 versus 21 months, $p < 0.01$), there was no difference of the time to hCG level normalization after starting chemotherapy (median 6 versus 7 months, $p = 0.65$) and most importantly, there was not a single case of relapse or death in either group.

Table 4 presents predictors of needing chemotherapy to achieve remission among Brazilian women with nonmetastatic GCC followed initially with expectant management. The analysis showed that the patients that are expected to have a smaller chance of needing chemotherapy after initial expectant management include: those with age ≤ 19 years (aOR 0,60; CI 95%: 0.51–0.99, $p = 0.03$), with antecedent ectopic pregnancy (aOR 0.25; CI 95%: 0.17–0.54, $p < 0.01$), with a time between the end of index pregnancy and arrival at the BRCGTD ≥ 8 weeks (aOR: 0.40; CI 95%: 0.24–0.69, $p = 0.02$), with falling hCG levels (aOR: 0.29; CI 95%: 0.16–0.51, $p = 0.02$) or normal hCG values (aOR: 0.09; CI 95%: 0.01–0.17, $p < 0.01$) on arrival at the

Table 1
Characteristics of Brazilian women with nonmetastatic gestational choriocarcinoma.

Variables	Immediately treated with chemotherapy per FIGO 2000 guidelines N = 152	Followed with expectant management *N* = 47	*p*-Value
Age, years[a]	30 (6.1; 20–48)	28 (6.8; 19–45)	0.79[b]
Gravidity, n[a]	2 (1.5; 1–6)	2 (1.8; 1–5)	0.92[b]
Parity, n[a]	1 (1.8; 0–5)	1 (1.2; 0–4)	0.89[b]
Antecedent pregnancy, n (%)			
• *Molar pregnancy*	68 (44.7)	22 (46.8)	0.88[b]
• *Preterm or term gestation*	49 (32.2)	15 (32)	0.76[b]
• *Abortion*	31 (20.4)	9 (19.1)	0.93[b]
• *Ectopic pregnancy*	4 (2.7)	1 (2)	0.78[c]
Clinical presentation, n (%)			
• *Anemia*	15 (9.8)	5 (10.6)	0.83[c]
• *Hemorrhage*	31 (20.4)	11 (23.4)	0.67[c]
• *Enlarged uterus for gestational age*	33 (21.7)	9 (19.1)	0.59[c]
• *Theca lutein cysts*	34 (22.3)	8 (17)	0.22[c]
• *Preeclampsia*	3 (2)	1 (2)	0.99[c]
• *Hyperemesis*	7 (4.6)	2 (4)	0.77[c]
• *Hyperthyroidism*	3 (2)	1 (2)	0.96[c]
• *Respiratory distress syndrome*	3 (2)	1 (2)	0.91[c]
hCG at diagnosis of choriocarcinoma. IU/L[a]	55,678 (23,122; 0–181,332)	68,399 (20,344; 0–201,611)	0.13[d]
Time between the end of index pregnancy and arrival at the RC (weeks)[a]	6 (5; 4–29)	7 (6; 5–30)	0.75[d]
hCG trend on arrival to the RC, n (%)			
• *Elevated*	72 (47.4)	21 (44.7)	0.86[c]
• *Falling*	49 (32.2)	14 (29.8)	0.63[c]
• *Normal*	31 (20.4)	12 (25.5)	0.39[c]

hCG - human chorionic gonadotropin.
RC – Reference Center for gestational trophoblastic disease.
[a] median (standard deviation; range).
[b] Student's *t*-test.
[c] Chi-square test.
[d] Mann-Whitney *U* test.

BRCGTD. The risk factors for needing chemotherapy after initial expectant management were age ≥ 40 years (aOR 1.67; 1,34–1.90, $p = 0.02$) and hCG level at diagnosis of choriocarcinoma ≥ 92,428 IU/L (aOR 5.82; CI 95%: 4.12–7.89, $p < 0.01$).

4. Discussion

We have shown that it appears to be safe to closely follow patients with a diagnosis of nonmetastatic GCC. With expectant management,

Table 2
Treatment and outcomes of Brazilian women with nonmetastatic gestational choriocarcinoma.

Variables	Immediately treated with chemotherapy per FIGO 2000 guidelines N = 152	Followed with expectant management N = 47	*p*-Value
Treatment with chemotherapy, n (%)	152 (100)	21 (44.7)	<0.01[e]
First line chemotherapy, n (%)			
• *Methotrexate with folinic acid rescue*[b]	134 (88.2)	18 (85.7)	0.89[e]
○ *Number of cycles*[a]	6 (2.1; 3–7)	5 (1.8; 3–7)	0.34[e]
• *Actinomycin-D*[c]	11 (7.2)	2 (9.5)	0.41[e]
○ *Number of cycles*[a]	4 (1.2; 3–6)	3 (0.7; 2–5)	0.57[e]
• *EMA/CO*	7 (4.6)	1 (4.7)	0.96[e]
○ *Number of cycles*[a]	2 (1; 2–4)	2 (0.8; 2–4)	0.86[e]
Second line chemotherapy, n (%)			
• *Actinomycin-D*[c]	10 (62.5)	1 (50)	0.78[e]
○ *Number of cycles*[a]	3 (1.7; 3–6)	3 (0; 3–3)	0.84[e]
• *EMA/CO*	6 (37.5)	1 (50)	0.09[e]
○ *Number of cycles*[a]	3 (1; 2–4)	3 (0; 3–3)	0.98[e]
Need of hysterectomy, n (%)	12 (7.9)	0 (0)	<0.01[g]
Indication for hysterectomy, n (%)			
• *Adjuvant surgery performed outside of reference center*	12 (7.9)	0 (0)	<0.01[e]
• *Chemoresistance*	0 (0)	0 (0)	1[e]
Time to hCG level normalization[a]	6 (2; 0–13)	11 (1.8; 0–19)	0.04[f]
Duration of follow up, months[a]	14 (1.3; 12–18)	19 (1; 12–23)	0.02[d]
Occurrence of relapse or death, n (%)	0 (0)	0 (0)	1[g]

hCG - human chorionic gonadotropin.
WHO/FIGO – World Health Organization/International Federation of Gynecology and Obstetrics.
[a] median (standard deviation; range).
[b] 8 day Methotrexate intramuscular 1 mg/kg on days 1, 3, 5 and 7 with rescue with folinic acid per orally 0.1 mg/kg on days 2, 4, 6 and 8.
[c] Actinomycin-D (Act-D) 1.25 mg intravenous pulse every 15 days EMA/CO – Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, Oncovorin® (Vincristine).
[d] Student's *t*-test.
[e] Chi-square test.
[f] Mann-Whitney *U* test.
[g] Fisher's Exact test.

Table 3
Comparison of Brazilian women with nonmetastatic gestational choriocarcinoma treated with chemotherapy, either per FIGO 2000 guideline (start chemotherapy immediately after histologic diagnosis of choriocarcinoma) or later due to plateau or elevation of human chorionic gonadotropin levels after an initial expectant management.

Variables	Indication for chemotherapy		*p*-Value
	Immediately treated with chemotherapy per FIGO 2000 guidelines $N = 152$	Treated later, due to plateau or elevation of hCG after expectant management $N = 21$	
Age, years[a]	30 (6.1; 20–48)	29 (4.3; 21–41)	0.75[b]
Antecedent pregnancy, n (%)			
• *Molar pregnancy*	68 (44.7)	15 (71.4)	0.10[b]
• *Preterm or term gestation*	49 (32.2)	4 (19)	0.21[b]
• *Abortion*	31 (20.4)	2 (9.6)	0.09[b]
• *Ectopic pregnancy*	4 (2.7)	0	0.04[c]
Time between the end of index pregnancy and arrival at the RC, weeks[a]	6 (5; 4–29)	8 (6; 6–30)	0.33[b]
Time to start chemotherapy after termination of pregnancy, weeks[a]	7 (4; 6–29)	10 (5; 8–30)	0.02[b]
hCG level at diagnosis of choriocarcinoma, IU/L[a]	55,678 (23,122; 0–181,332)	92,428 (15,916; 911–201,611)	0.02[d]
WHO/FIGO Prognostic Risk Score[a]	4 (1.1; 1–7)	4 (1.4; 1–7)	0.73[b]
WHO/FIGO Prognostic Risk Score ≥ 7, n (%)	7 (4.6)	1 (4.7)	0.89[e]
Chemotherapy treatment with multi-agent regimen, n (%)	13 (8.5)	1 (4.7)	0.14[e]
Number of chemotherapy cycles to remission, n (%)[a]	6 (1.9; 3–7)	6 (1.4; 3–7)	0.91[b]
Development of metastasis, n (%)	7 (4.6)	1 (4.7)	0.87[e]
Development of chemoresistance, n (%)	16 (10.5%)	2 (9.5)	0.94[c]
Time to hCG level normalization after starting chemotherapy, weeks[a]	6 (2; 0–13)	7 (2.5; 1–13)	0.65[d]
Duration of follow up, months[a]	14 (1.3; 12–18)	21 (3; 12–23)	<0.01[b]
Occurrence of relapse or death, n (%)	0	0	1[e]

hCG - human chorionic gonadotropin.
WHO/FIGO – World Health Organization/International Federation of Gynecology and Obstetrics.
RC – Reference Center for gestational trophoblastic disease.
[a] median (standard deviation; range).
[b] Student's t-test.
[c] Chi-square test.
[d] Mann-Whitney *U* test.
[e] Fisher's Exact test.

we were able to avoid chemotherapy exposure to over half of our patients without the development of more advanced disease, greater need of multi-agent chemotherapy or in any case of death or relapse. While withholding immediate chemotherapy from women with a histologic diagnosis of choriocarcinoma may contravene current FIGO guidelines [9], our observation of the safety of this approach is similar to other reports [12–20].

Pathological diagnosis of GCC in specimens from uterine evacuations following molar pregnancies or abortions, salpingectomies in suspected ectopic pregnancies, or even placentas of preterm or term deliveries are not promptly available for Brazilian patients and physicians in the public health system – taking generally 6–7 weeks for the final pathological results. Patients who receive these results are referred to a BRCGTD, where 1–2 additional weeks are needed for pathological review and specialized evaluation of the specimens. The delayed evaluation of these patients resulted in 21.6% (43/199) of women with GCC to achieve normal hCG values with no treatment by the time diagnosis was established and care initiated at the BRCGTD. All patients with expectant management that presented with normal hCG levels at the initial evaluation at the BRCGTD (12 patients) achieved complete sustained remission without chemotherapy.

The current FIGO recommendation to treat all patients with a histological diagnosis of choriocarcinoma, including cases with normal hCG, seems unnecessarily to treat more than half of patients with nonmetastatic disease according to the findings in the current study. While expectant management for at least two to three weeks after patients were referred to one of the specialized centers increased the time to initiate chemotherapy, it did not lead to a worse outcome, since the WHO/FIGO score, the rate of high risk GTN and the need of multi-agent chemotherapy were comparable to patients who started immediate chemotherapy following the diagnosis of choriocarcinoma. Additionally, patients under initial expectant management did not experience more metastatic disease, chemoresistance or any case of relapse or death.

Among patients that chose expectant management, those that were ≤19 years old were less likely to need chemotherapy; while women ≥40 years old were more likely to need chemotherapy. Age seems to be an important prognostic factor for patients with GTN, since advanced maternal age has been associated with increased progression to postmolar GTN and immunological factors may play a role in these processes [22,23]. Salpingectomy for ectopic pregnancy was also associated with spontaneous remission, likely because the removal of the Fallopian tube completely resected the tumor. It is important to be highlighted that patients with diagnosis of GCC who adopted expectant management and eventually required chemotherapy had a longer follow up time than those who received immediate chemotherapy (21 vs. 14 months). This may have some effect on patients having delayed future pregnancy and should be emphasized on the occasion of informed consent for guidance on expectant management among patients with GCC.

The main limitation of this study was its retrospective nature and absence of randomization of treatments. Also data were collected from different hospital databases and may not represent the Brazilian general population. As referral centers, the prevalence of GCC may be overestimated in this study and probably does not reflect the true frequency of this condition. Despite investigating a comparatively large series of patients with GCC, only 47 patients chose expectant management, and this may bias our results. However, we are not aware of any other published report related to this issue with a comparable number of patients. Finally, we recognize that patients with GCC undergoing hysterectomy have a better prognosis, which could overestimate the good results of the treatment [24]. However, all patients who

Table 4
Predictors of needing chemotherapy to achieve remission among Brazilian women with nonmetastatic gestational choriocarcinoma followed initially with expectant management.

Variables	Odds ratio for requiring chemotherapy			
	cOR (CI 95%)	*p*-Value[a]	aOR (CI 95%)	*p*-Value[a]
Age				
• *20–39*	1.0 (Ref)		1.0 (Ref)	
• *≤19*	0.68 (0.54–0.91)	0.04	0.60 (0.51–0.99)	0.03
• *≥40*	1.45 (1.24–4.31)	0.03	1.67 (1.34–1.90)	0.02
Gravidity	0.87 (0.78–1.31)	0.21	0.91 (0.81–1.39)	0.20
Parity	0.90 (0.81–1.52)	0.81	0.91 (0.83–1.61)	0.84
Antecedent pregnancy, n (%)				
• *Molar pregnancy*	1.0 (Ref)		1.0 (Ref)	
• *Term gestation*	1.47 (0.85–1.98)	0.15	1.54 (0.89–1.99)	0.11
• *Abortion*	0.68 (0.45–1.09)	0.18	0.88 (0.65–1.14)	0.22
• *Ectopic pregnancy*	0.38 (0.29–0.67)	< 0.01	0.25 (0.17–0.54)	< 0.01
Clinical presentation				
• *Anemia*	1.34 (0.87–1.68)	0.28	1.44 (0.89–1.72)	0.27
• *Hemorrhage*	1.29 (0.77–1.55)	0.31	1.37 (0.81–1.67)	0.30
• *Enlarged uterus for gestational age*	1.78 (0.65–1.93)	0.21	1.80 (0.70–1.99)	0.19
• *Theca lutein cysts*	1.08 (0.76–1.15)	0.47	1.12 (0.79–1.23)	0.41
• *Preeclampsia*	1.45 (0.88–1.91)	0.32	1.56 (0.90–1.99)	0.29
• *Hyperemesis*	1.19 (0.69–1.54)	0.55	1.30 (0.70–1.60)	0.51
• *Hyperthyroidism*	1.68 (1.10–1.89)	0.04	1.35 (0.89–1.56)	0.09
• *Respiratory distress syndrome*	1.14 (0.89–1.59)	0.24	1.40 (0.91–1.68)	0.10
hCG level at diagnosis of choriocarcinoma ≥92,428	4.56 (3.12–6.78)	<0.01	5.82 (4.12–7.89)	<0.01
Time between the end of index pregnancy and arrival at the RC ≥ 8 weeks	0.44 (0.25–0.75)	0.03	0.40 (0.24–0.69)	0.02
hCG trend on arrival to the RC				
• *Elevated*	1.0 (Ref)		1.0 (Ref)	
• *Falling*	0.45 (0.21–0.78)	0.04	0.29 (0.16–0.51)	0.02
• *Normal*	0.15 (0.02–0.25)	<0.01	0.09 (0.01–0.17)	<0.01

hCG - human chorionic gonadotropin (IU/L).
RC – Reference Center for gestational trophoblastic disease.
cOR – crude odds ratio.
aOR – adjusted odds ratio.
[a] Wald test for logistic regression. Adjusted by age group, origin of choriocarcinoma, hCG level at diagnosis of choriocarcinoma, time between surgery and arrival at the RC and feature of hCG on arrival at the RC.

underwent hysterectomy in this cohort were subsequently treated with adjuvant chemotherapy, none of them belonging to the patient group under expectant management.

In conclusion, in settings where patients with nonmetastatic GCC can be closely followed with hormonal and radiological surveillance, it may be appropriate to consider expectant management, since 55.3% of these women will have their hCG levels fall to normal range spontaneously. Continued surveillance avoids exposing women unnecessarily to potential toxicities of chemotherapy [4,5,1]. Moreover, patients with nonmetastatic GCC, who were initially monitored with hCG surveillance and experienced a hCG rise or plateau had similar outcomes to patients who received immediate chemotherapy. Therefore, based on the results of this study it seems reasonable to consider close surveillance with hCG monitoring of patients with a pathological diagnosis of gestational choriocarcinoma who have no evidence of metastasis and falling or normal hCG levels without immediately initiating chemotherapy. It would be very helpful if other centers would review their data related to this clinical issue. If confirmed, the FIGO guidelines may need to be revised.

Disclosures

The authors report no conflicts of interest.

Funding

This research was supported by the Carlos Chagas Filho Foundation for Research Support in the State of Rio de Janeiro/Brazil (FAPERJ) (E-26/112.070/2012) – an agency under the Brazilian Ministry of Science and Technology; and the Donald P. Goldstein MD Trophoblastic Tumor Registry Endowment and the Dyett Family Trophoblastic Disease Research and Registry Endowment. The funding agencies had no direct role in the generation of the data or manuscript.

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