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GestaTIonal TrophoblAstic Neoplasla Ultrasound assessMent: TITANIUM study

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ABSTRACT

Background There are limited data on ultrasound morphologic features of gestational trophoblastic neoplasia. A predictive model to determine predictors of response to therapy would be ideal in the management of patients with this rare disease.

Primary Objectives and Study Hypothesis TITANIUM is a prospective, multicenter, observational study aiming to describe ultrasound features of gestational trophoblastic neoplasia and to investigate the role of ultrasound in identifying patients at high risk of resistance to single-drug therapy. The study hypothesis is that ultrasound could improve the International Federation of Gynecology and Obstetrics (FIGO) scoring system for early identification of patients predisposed to single-drug resistance.

Trial Design and Major Inclusion/Exclusion Criteria Patients eligible have a diagnosis of gestational trophoblastic neoplasia according to FIGO or the criteria set by Charing Cross Hospital, London, UK. At diagnosis, patients are classified as low-risk (score 0–6) or high-risk (score >6) according to the FIGO risk scoring system, and a baseline ultrasound scan is performed. Patients receive treatment according to local protocol at each institution. Follow-up ultrasound examinations are performed at 1, 4, 10, 16, and 22 months after start of chemotherapy, and at each scan, serum human chorionic gonadotropin (hCG) level, and chemotherapy treatment, if any, are recorded.

Primary Endpoints Our aims are to define ultrasound features of gestational trophoblastic neoplasia and to develop a predictive model of resistance to single-drug therapy in low-risk patients.

Sample Size The sample size was calculated assuming that 70% of patients with gestational trophoblastic neoplasia are at low risk, and estimating the rate of resistance to single-drug therapy in this group to be 40%. Assuming a dropout rate of 10%, we should recruit at least 120 patients. With this sample size, we can attempt to create a mathematical model with three variables (either two ultrasound parameters in addition to the risk score or three ultrasound variables statistically significant at univariate analysis) to predict resistance to single-drug therapy in low-risk patients.

Estimated Dates for Completing Accrual and Presenting Results The accrual started in February 2019. Additional referral centers for gestational trophoblastic disease, with similar ultrasound expertise, are welcome to participate in the study. Enrollment should be completed by December 2021, and analysis will be conducted in December 2023.

Trial Registration The study received the Ethical Committee approval of the Coordinator Center (Rome) in January 2019 (Protocol No. 0004668/19).

INTRODUCTION

Gestational trophoblastic disease is a group of pre-malignant (partial or complete hydatidiform mole) and malignant disorders (invasive hydatidiform mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor) arising from abnormal trophoblastic tissue proliferation during or after any type of pregnancy. The malignant forms are also known as gestational trophoblastic neoplasia. Gestational trophoblastic disorders are rare tumors that account for fewer than 1% of gynecologic malignancies.[1]

The diagnosis of gestational trophoblastic neoplasia is made using the International Federation of Gynecology and Obstetrics (FIGO) criteria[2] or the Charing Cross Hospital (London, UK) criteria.[3] Only approximately 50% of gestational trophoblastic neoplasia follows as a result of a molar pregnancy and is diagnosed by serum human chorionic gonadotropin (hCG) surveillance (post-molar gestational trophoblastic neoplasia). The rest of the reported cases of gestational trophoblastic neoplasia may occur after spontaneous abortion, ectopic pregnancy, or term pregnancy, where no routine hCG monitoring is recommended. It is therefore essential to consider gestational trophoblastic neoplasia in any woman of childbearing age with irregular vaginal bleeding or who has unexplained metastatic disease or acute symptoms compatible with metastases in lungs, brain, gastrointestinal, or urinary tracts.

Treatment of gestational trophoblastic neoplasia is generally by chemotherapy and the treatment regimen depends on stage and classification. The therapeutic regimens are chosen based on the FIGO and WHO prognostic scoring system (Table 1).[4 5] Most patients with gestational trophoblastic neoplasia who are diagnosed with a risk score of 0–6 are considered at low risk of chemoresistance to single-drug therapy (70%–80%).[6] There are numerous effective chemotherapeutic regimens used worldwide for the treatment of low-risk gestational trophoblastic neoplasia; however, those most commonly used are either methotrexate or actinomycin-D, as single agent.

Table 1 International Federation of Gynecology and Obstetrics (FIGO)/World Health Organization (WHO) (2000) risk factor scoring system for gestational trophoblastic neoplasia.

	Score			
Prognostic factor	**0**	**1**	**2**	**4**
Age (years)	<40	≥40	–	–
Antecedent pregnancy (AP)	Mole	Abortion	Term	–
Interval (end of AP to chemotherapy in months)	<4	4–6	7–12	>12
Human chorionic gonadotropin (IU/L)	$<10^3$	$>10^3$–10^4	$>10^4$–10^5	$>10^5$
Metastases (n)	0	1–4	5–8	>8
Site of metastases	No metastases or only lung	Spleen, kidney	Gastrointestinal tract	Liver, brain
Largest tumor mass (cm)	–	3–4	>5	–
Prior chemotherapy	–	–	Single drug	≥2 drugs

The total score is obtained by adding the individual scores for each prognostic factor. Low-risk, 0–6; high-risk,>6. Placental site trophoblastic tumor and epithelioid trophoblastic tumor should not be scored and instead require staging: stage I, disease confined to the uterus; stage II, disease extended to the pelvis; stage III, disease spread to lung and/or vagina; stage IV, all other metastatic sites including liver, kidney, spleen, and brain.

Most low-risk women will be cured by chemotherapy regardless of the regimen used; however, reported primary remission rates vary, and up to 40% of affected women may require additional therapy due to failure of first-line single-agent chemotherapy.[7] Patients with a risk score >6 are considered at high risk of resistance to single-drug therapy, and in these patients, multiple-agent chemotherapy regimens are required.[8] The most commonly used regimen is the combination of etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMACO), although a Cochrane Review failed to conclude what combination was the best.[9]

Placental-site trophoblastic tumor and epithelioid trophoblastic tumor should not be scored and instead require staging according to the FIGO 2000 classification. Surgical resection remains the primary treatment for placental-site trophoblastic tumor and epithelioid trophoblastic tumor, followed by multi-agent adjuvant chemotherapy according to prognostic factors and disease stage.[10]

In the literature, there are very few data on ultrasound morphologic features of gestational trophoblastic neoplasia. Several studies have suggested that the amount of tumor vascularization, as detected on Doppler ultrasonography, could add information to the FIGO scoring system for the early identification of those low-risk patients who will need second-line therapy. It has been suggested that uterine artery pulsatility index is an independent risk factor for resistance to single-agent methotrexate therapy in low-risk gestational trophoblastic neoplasia.[11–14]

Our prospective multicenter cohort study aims to describe ultrasound morphologic features of gestational trophoblastic neoplasia and to investigate the role of ultrasound in identifying patients with a risk score <6 who are at high risk of resistance to single-drug therapy. The study hypothesis is that ultrasound parameters could improve the FIGO risk scoring system in predicting resistance to single-drug therapy in such a group of patients.

METHODS AND ANALYSIS

Study Design

The TITANIUM study is designed as an international, multicenter, prospective, observational study with the primary objectives being to describe typical ultrasound features of gestational trophoblastic neoplasia and to identify ultrasound predictors of resistance to single-drug chemotherapy in low-risk patients. A schematic description of the study is shown in Figure 1.

Data collection and management will be supported by the web-based REDCap software and by the STAR (Statistics Technology Archiving Research) Center at the A. Gemelli Hospital in Rome, Italy.

Investigations will include transvaginal ultrasound examination and serum hCG at initial diagnosis, as well as during follow-up after the start of chemotherapy. At each scan all the ultrasound parameters listed in Box 1 will be evaluated. Moreover, a computed tomography (CT) scan of brain, chest, and abdomen is required for staging, prior to the start of chemotherapy. At the diagnosis of gestational trophoblastic neoplasia, patients will be classified as low- or high-risk for resistance to single-drug therapy using a FIGO risk score of ≤6 or >6, and a baseline ultrasound scan will be performed. Patients will receive treatment according to the local protocol of each institution and such treatment will be documented.

Follow-up ultrasound examinations will be performed at 1, 4, 10, 16, and 22 months after start of chemotherapy. These five follow-up scans will be performed as long as there is a persistent lesion, even if the hCG is negative. After the previously documented lesion has disappeared, further scans will not be indicated. Even after its normalization, hCG should be examined every 6 months until the lesion has disappeared on ultrasound. If the lesion is still visible at the 22 months ultrasound scan, despite negative hCG levels, additional ultrasound scans will be performed every 6 months until the disappearance of the lesion (or until the study is stopped, that is when all the patients included have been followed up for at least 22 months).

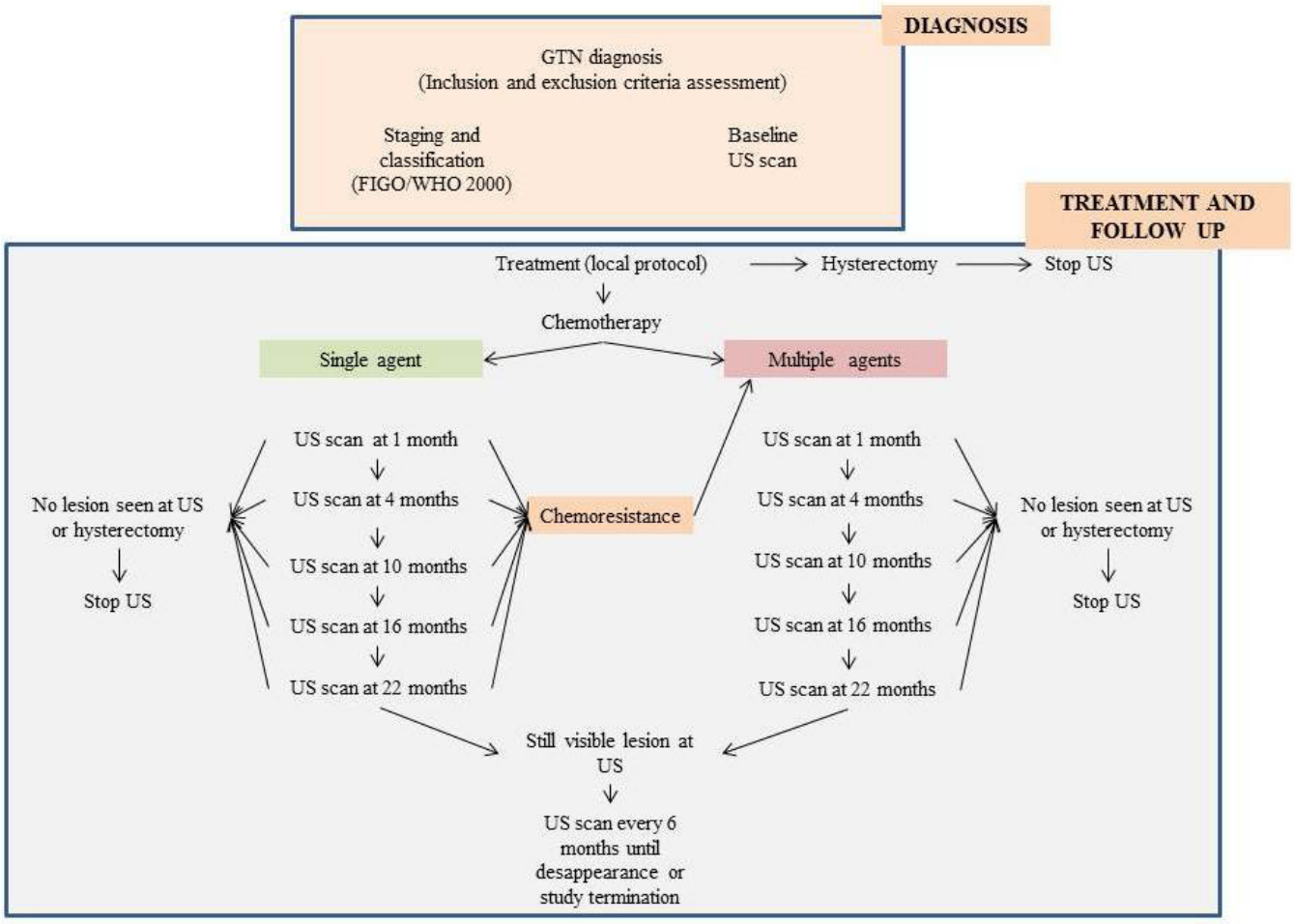

Figure 1 TITANIUM study algorithm. FIGO, International Federation of Gynecology and Obstetrics; GTN, gestational trophoblastic neoplasia; US, ultrasound; WHO, World Health Organization.

The minimum requirements for any center to participate will include: (a) referral center for gestational trophoblastic disease in which patients are usually assessed with ultrasound; (b) experienced ultrasound examiners; (c) at least five cases of gestational trophoblastic neoplasia managed in the center each year; (d) adherence to the study protocol; and (e) local ethical committee approval. No funding has been provided for the research project.

Participants

Patients will be enrolled in the study if a diagnosis of gestational trophoblastic neoplasia is made according to any of the following FIGO 2000 criteria or Charing Cross Hospital (London, UK) criteria: (a) histologic diagnosis of placental-site trophoblastic tumor or epithelioid trophoblastic tumor; (b) histologic evidence of invasive mole or choriocarcinoma; (c) rising hCG after evacuation of hydatidiform mole, that is, two consecutive rises in hCG of 10% or greater over at least 2 weeks; (d) plateau of hCG after evacuation of hydatidiform mole, that is, four or more equivalent values of hCG over at least 3 weeks; (e) hCG level remaining elevated for 6 months or more after evacuation, even if decreasing; (f) heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal hemorrhage in patients with histologic diagnosis of gestational trophoblastic disease; (g) serum hCG concentration of 20 000 IU/L or more, 4 weeks or more after evacuation of a mole; or (h) evidence of metastases in brain, liver, or gastrointestinal tract, or radiologic opacities larger than 2 cm on chest radiograph in patients with gestational trophoblastic disease. All patients must have provided signed informed consent. Previous or ongoing chemotherapy for gestational trophoblastic neoplasia or refusal to sign informed consent are exclusion criteria.

Outcomes

The primary objectives are: (a) to describe gray-scale and color Doppler ultrasound features of gestational trophoblastic neoplasia at baseline ultrasound examination; (b) to assess if there are any differences at the baseline ultrasound scan between low-risk and high-risk patients and, in the low-risk group, between the subgroups of responders and non-responders to single-drug therapy; (c) to identify ultrasound predictors of resistance to first-line single-drug chemotherapy in low-risk gestational trophoblastic neoplasia; and (d) to create a multivariable logistic regression model to predict resistance to single-drug therapy in low-risk patients.

Secondary objectives are to describe any longitudinal changes in ultrasound characteristics of gestational trophoblastic neoplasia during treatment and after stopping treatment, the latter in cured patients with still-visible uterine lesion at ultrasound, despite the normalization of hCG.

Box 1. Ultrasound parameters evaluated at each scan in patients with gestational trophoblastic neoplasia.

Size of the uterine lesion

Echogenicity of the lesion (if a lesion is visible)

- Focal lesion with different echogenicity from the surrounding myometrium, without vascularization
- Focal lesion with different echogenicity from the surrounding myometrium, with vascularization but no suspicion of arteriovenous malformation
- Focal lesion with different echogenicity from the surrounding myometrium, with vascularization and an image suggestive of arteriovenous malformation confirmed with color and spectral Doppler
- Global lesion without vascularization
- Global lesion with vascularization but no suspicion of arteriovenous malformation
- Global lesion with vascularization and at least one area with suspicion of arteriovenous malformation confirmed on color and spectral Doppler

Color score of the lesion (according to IOTA and IETA terminology) on color Doppler

- 1: no flow
- 2: sparse flow
- 3: moderate flow
- 4: abundant flow

Peak systolic velocity (PSV) (cm/s) measured in arteriovenous malformation (only if arteriovenous malformation is suspected) on spectral Doppler

Pulsatility index (PI) and PSV (cm/s) in both uterine arteries on spectral Doppler

Presence or absence of theca lutein cyst in both ovaries

IETA, International Endometrial Tumor Analysis; IOTA, International Ovarian Tumor Analysis.

Sample Size

The sample size was calculated to allow the creation of a multivariable logistic regression model including three variables to predict non-response to single-drug therapy in patients with low-risk gestational trophoblastic neoplasia. We assume 70% of patients with gestational trophoblastic neoplasia to be low-risk patients, and 40% of the low-risk patients to be resistant to single-drug therapy. We estimate a 10% dropout rate. Researchers suggest that when using multivariate logistic regression analysis to create a prediction model there should be at least 10 events per variable.[15] According to this, considering a model with three variables (either two ultrasound parameters in addition to the risk score, or three ultrasound variables statistically significant in univariate analysis), we should recruit at least 120 patients (120 minus 0.10×120=108; 0.7×108=76 low-risk patients; 0.40×76=30 low-risk patients with gestational trophoblastic neoplasia not responding to single-drug therapy).

Statistical Methods

The statistical analysis will include only patients whose images have been stored on the web-based database for later review. For the analysis, we will identify two groups according to the FIGO risk score: low-risk (score 0–6) and high-risk (score >6) groups. Moreover, in the low-risk group, patients will be grouped according to chemotherapy response: responders versus non-responders to single-agent chemotherapy. For aims (a) and (b), all parameters collected at the baseline ultrasound examination will be presented and analyzed in terms of listings and summary tables with numbers (percentage) or median (range) as appropriate.

Clinical and ultrasound features at the baseline ultrasound scan of all patients will be analyzed to assess if there are differences between low-risk and high-risk patients, and in the low-risk group, between responders and non-responders to the first-line single-drug chemotherapy.

Mann–Whitney U test (for continuous variables) and Chi-square or Fisher's exact test (for categorical variables) as appropriate will be used to assess if there are statistically significant differences in patient and ultrasound characteristics between the low-risk and high-risk groups.

The ability of clinical and sonographic characteristics of low-risk patients to predict non-response to single-agent drug therapy will be assessed using univariable logistic regression analysis. Moreover, we plan to explore the possibility of creating a model to predict chemoresistance by using multivariate logistic regression analysis.

For secondary aims, a longitudinal analysis of clinical and sonographic parameters collected at the baseline scan (time 0), during chemotherapy (time 1) and after the end of treatment (time 2) will be performed for low-risk patients according to chemotherapy resistance development (responders to a single-drug therapy versus non-responders). Data will be presented with boxplots and histograms for continuous and categorical variables, respectively. Two-sided statistical tests will be used and the significance level will be set at $p<0.05$. We expect the longitudinal change in ultrasound parameters in high-risk patients to be very heterogeneous. If our assumption is confirmed, we will describe each case separately in a table or with graphs as appropriate.

DISCUSSION

The TITANIUM study is an international, multicenter, observational, prospective study that aims to describe ultrasound features of gestational trophoblastic neoplasia and to identify ultrasound predictors of resistance to single-drug chemotherapy in low-risk patients. The protocol has been developed to be non-interventional and to reflect clinical practice at institutions in which patients with gestational trophoblastic neoplasia are assessed with ultrasound. Patients receiving any kind of treatment (surgery or chemotherapy and all regimens of chemotherapy) are eligible for the study and patients will be treated according to local protocols. Low-risk patients (FIGO risk score $\leq$6) are treated with single-drug chemotherapy but may require additional agents, with scores of 5–6 being associated with higher drug resistance.[16] We explore the possibility of identifying ultrasound predictors of resistance to single-drug therapy in low-risk gestational trophoblastic neoplasia and to create a mathematical model to predict drug resistance in this group of patients. This could potentially improve the FIGO risk scoring system for selecting patients who could benefit from multiple-agent therapy from the beginning of the treatment.

Patient enrolment started in February 2019 at the Fondazione Policlinico Universitario A. Gemelli IRCCS in Rome and is due to start

soon at three other institutions: San Gerardo Hospital in Monza, Skåne University Hospital in Malmö, and Södersjukhuset (KI-SÖS) in Stockholm. We consider that at least 10 referral centers for gestational trophoblastic disease will participate in the study. Assuming 5–10 new cases of gestational trophoblastic neoplasia per year for each institution, the target accrual of 120 patients should be reached by the end of 2021, and the analysis of patients followed up for 22 months should be conducted by the end of 2023.

Contributors DV: study conception and design, data collection, monitoring data, analysis and interpretation of data, writing the manuscript, critical revision of the manuscript, final approval. TP: study conception and design, development of the web-based platform for data collection, monitoring data, analysis and interpretation of data, writing the manuscript, critical revision of the manuscript, final approval. EE: study conception and design, data collection, analysis and interpretation of data, writing the manuscript, critical revision of the manuscript, final approval. RF: study conception and design, data collection, analysis and interpretation of data, writing the manuscript, critical revision of the manuscript, final approval. FM: study conception and design, data collection, critical revision of the manuscript, final approval. FM: study conception and design, data collection, critical revision of the manuscript, final approval. GS: study conception and design, analysis and interpretation of data, critical revision of the manuscript, final approval. LV: study conception and design, data collection, analysis and interpretation of data, writing the manuscript, critical revision of the manuscript, final approval. ACT: study conception and design, data collection, analysis and interpretation of data, writing the manuscript, critical revision of the manuscript, final approval.

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