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# Relationship between race and clinical characteristics, extent of disease, and response to chemotherapy in patients with low-risk gestational trophoblastic neoplasia

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## HIGHLIGHTS

- Among patients with low-risk gestational trophoblastic neoplasia, African Americans were significantly younger and had more children than whites and Asians.
- Extent of low-risk gestational trophoblastic neoplasia was comparable among races as reflected in stage, FIGO score, and pretreatment hCG level.
- Low-risk GTN was more aggressive in Asians, who were more likely to require a second line regimen to achieve remission.

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## ABSTRACT

*Objective.* To evaluate the potential effects of race on clinical characteristics, extent of disease, and response to chemotherapy in women with postmolar low-risk gestational trophoblastic neoplasia (GTN).

*Methods.* This non-concurrent cohort study was undertaken including patients with FIGO-defined postmolar low-risk GTN treated with comparable doses and schedules of chemotherapy at the New England Trophoblastic Disease Center (NETDC) between 1973 and 2012. Racial groups investigated included whites, African American and Asians. Information on patient characteristics and response to chemotherapy (need for second line chemotherapy, reason for changing to an alternative chemotherapy, number of cycles/regimens, need for combination chemotherapy, and time to hCG remission) was obtained.

*Results.* Of 316 women, 274 (86.7%) were white, 19 (6%) African American, and 23 (7.3%) Asian. African Americans were significantly younger than white and Asian women ($p = 0.008$). Disease presentation, and extent of disease, including antecedent molar histology, median time to persistence, median hCG level at persistence, rate of D&C at persistence, presence of metastatic disease, and FIGO stage and risk score were similar among races. Need for second line chemotherapy ($p = 0.023$), and median number of regimens ($p = 0.035$) were greater in Asian women than in other races.

*Conclusions.* Low-risk GTN was more aggressive in Asian women, who were significantly more likely to need second line chemotherapy and a higher number of chemotherapy regimens to achieve complete remission than women of African American and Asian descent. Further studies involving racial differences related to clinical, biological and environmental characteristics are needed.

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## 1. Introduction

Gestational trophoblastic disease (GTD) is a group of interrelated but histologically distinct tumors originating from the placenta. Persistent GTD, most commonly defined as a persistent elevation of human chorionic gonadotrophin (hCG), arises from a molar pregnancy in over 50% of

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the cases. This condition is referred to as gestational trophoblastic neoplasia (GTN). The risk of developing GTN after a complete hydatidiform mole (CHM) and a partial hydatidiform mole (PHM) is about 15–20% and 1–4%, respectively [1–3].

Significant regional and racial differences in the incidence of hydatidiform mole have been reported worldwide. These differences are partially attributable to discrepancies between population-based and hospital-based data collection [4]. The reported incidence is 1 in 1000 live births in Europe, 1 in 1500 in the United States, and as high as 2 in 1000 pregnancies in South East Asia and Japan [5]. Internationally, incidence rates have declined over the past 30 years in most populations [2]. However, Native Americans and women of Asian descent reportedly have an increased incidence [4,6,7].

According to a combined anatomic staging and scoring system, based on the International Federation of Gynecology and Obstetrics (FIGO, 2002) [8] and modified World Health Organization (WHO) risk-factor scoring system, FIGO stages I–III with a score of 0–6 identify low-risk GTN. However, either FIGO stage IV or any stage with a WHO score $\geq 7$ indicates high-risk of resistance to single-agent chemotherapy, increased risk of recurrence, and the need for combination chemotherapy to optimize outcome.

GTN is highly responsive to chemotherapy. Low-risk GTN is cured with single-agent chemotherapy with either methotrexate (MTX) or actinomycin-D (actD) in 90% of the cases, and with multiagent chemotherapy in the remaining 10% [9,10]. For patients with high-risk GTN, multiagent protocols are the primary treatment of choice [11].

Higher hCG levels [12,13], presence of metastatic disease [10,14], histologic diagnosis of complete mole [10,12], higher risk FIGO score [10,15,16], increasing neo-angiogenesis [17], and older patient age [18], have all been associated with increased risk of initial chemotherapy resistance and longer time to achieve remission in low-risk GTN patients.

Studies on racial disparities in cancer outcome have demonstrated that, compared with whites, minority groups in the United States are more likely to have a worse prognosis, and long-term survival significantly inferior for many types of cancer [19,20]. Such disparities in cancer outcomes have been attributed to socioeconomic status, cultural aspects, and differences in access to care and treatment patterns [21,22].

Moreover, ethnic diversity in chemotherapy response or toxicity has been recognized as an important factor accounting for inter-individual variation in anticancer therapy responsiveness. Indeed, there is consistent evidence that East Asian individuals are more susceptible to the effects of some chemotherapy agents than their Western counterparts [23,24]. Studies replicating, in Asian countries, clinical trials already done in the United States to determine optimal and tolerable dosing of new chemotherapy regimens in different types of cancer, found that although overall chemotherapy doses were reduced, the rate of disease response and toxicity were increased in Asian individuals [23].

The potential influence of race on GTN characteristics and outcomes remains unclear. To date, studies on GTN have not substantially focused on either specific racial groups or specific outcomes. Thus, the aim of this study was to evaluate the potential effects of race on clinical characteristics, extent of disease, and response to chemotherapy in women with postmolar low-risk GTN.

## 2. Methods

This non-concurrent cohort study included 442 patients with FIGO-defined postmolar low-risk GTN (stage I and stages II–III, score < 7) [8] treated at the New England Trophoblastic Disease Center (NETDC) between 1973 and 2012. Clinical, imaging, and laboratory assessments were performed as reported elsewhere [10,25]. Lung metastases were diagnosed by chest X-ray. When patients had pulmonary involvement, liver function abnormalities or symptoms suggestive of metastasis, a magnetic resonance imaging (MRI) or CT scan of the brain and abdomen/pelvis was performed. Dilatation and curettage (D&C) at persistence was defined as occurring within 7 days after GTN diagnosis.

First line therapy consisted of 8-day MTX/folinic acid [26], 1-day MTX infusion [27], weekly intramuscular MTX [28], 5-day actD [29], or biweekly pulsed intravenous actD [16] (Table 1). Complete response or remission was defined as normalization of serum hCG levels for 3 consecutive weeks and then monthly for 1 year. Patients were deemed to be resistant to single agent-therapy (either MTX or actD) if serum hCG plateaued for more than 3 consecutive weekly values, or if serum hCG increased. In cases of resistance to initial MTX or actD, either the alternative single agent therapy or multiagent regimens using MAC (MTX, actD, and cyclophosphamide) or EMA/CO (etoposide, MTX, actD, cyclophosphamide, and vincristine) were administered. After undetectable serum hCG levels were achieved, one to three courses of consolidation therapy were administered [25].

Chemotherapy dosing was calculated based on either actual body weight or body surface area (BSA) for all patients. However, actD dose was reduced to <1000 μg/day in 5-day actD regimens, or capped at a maximum of 2 mg in pulse regimens in order to avoid grade 3 or 4 toxicity.

Clinical data including age, race, history of prior mole, molar histology (complete or partial), time to persistence, pretreatment serum hCG level, use of D&C at persistence, presence of metastatic disease, stage, FIGO risk score, and type of first line therapy (MTX or actD) and response to chemotherapy were obtained. Race was self-reported as defined by the National Institutes of Health [30]. Time to persistence (days) was defined as the time between molar evacuation and postmolar GTN diagnosis.

Response to chemotherapy was assessed in terms of need for second line chemotherapy, reason for changing to an alternative chemotherapy (resistance/toxicity), number of cycles/regimens, need for combination chemotherapy, and time to hCG remission. Time to remission (days) was defined as the interval between postmolar GTN diagnosis and first normal serum hCG value. Most patients were followed using a serum hCG assay with a sensitivity of 5 mIU/mL, although a few patients treated prior to 1990 were followed with assays sensitive to 10 mIU/mL. Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Statistical analyses were carried out using SPSS statistical software (version 15.0, SPSS, Inc., Chicago, IL). Patient characteristics and treatment response across racial groups were compared using the chi-square test, Fisher's exact test, and Kruskal–Wallis test followed by the test of Dunn for multiple comparisons where appropriate. Significance level was set at $p < 0.05$.

This study was approved by the Institutional Committee of Human Research Ethics (# 2008P001321/BWH) at the Brigham and Women's Hospital.

## 3. Results

Of 442 women diagnosed with FIGO-defined postmolar GTN, 316 received first line single agent chemotherapy with either MTX or actD and were included in the analysis. The remaining 126 women were excluded for the following reasons: high-risk GTN diagnosis ($n = 10$), hysterectomy or surgical resection (29), chemoprophylaxis at the time of hydatidiform mole (21), hCG re-elevation due to recurrence (18), loss to follow-up (11), improper timing of chemotherapy administration (3), phantom hCG/quiescent disease diagnosis (2), primary treatment with combination chemotherapy (5), and unknown patient race (27).

The clinical characteristics of the 316 women included in the analysis are shown in Table 2. Two hundred seventy-four (86.7%) women were white, 19 (6%) were African American, and 23 (7.3%) were Asian. Median patient age was 28 years (range, 14–50 years). Compared to white and Asian women, African Americans were significantly younger ($p = 0.008$). Median parity was higher among African Americans than in the other races, but this difference was not statistically

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