Timing of Referral to the New England Trophoblastic Disease Center

Decentralized Treatment for Postmolar Gestational Trophoblastic Neoplasia is Associated with Increased Lines of Chemotherapy and Longer Time to Remission

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OBJECTIVE: To assess if referral before or after primary chemotherapy treatment for postmolar gestational trophoblastic neoplasia (PMGTN) affected subsequent clinical outcomes.

STUDY DESIGN: Records were queried retrospectively at the New England Trophoblastic Disease Center (NETDC) for all patients with PMGTN from 1993–2013 requiring >1 line of chemotherapy to achieve remission.

RESULTS: From 1993–2013 173 women were treated for PMGTN, and 65 required >1 line of chemotherapy and formed the study population. An increase in the need for >2 lines of chemotherapy was noted in the cohort referred after initial chemotherapy as compared to the cohort with treatment beginning at NETDC (9/18 [50%] vs. 7/40 [18%]; p=0.003); this difference remains significant when controlling for age, hCG at persistence, and WHO risk score (p=0.04). This translated into prolonged time to remission (78 vs. 107 days, p=0.01) on univariate analysis. Treatment at an outside institution was the variable most strongly associated with prolonged time to remission in a multivariate model (HR 0.54, 95% CI 0.27–1.07; p=0.08).

In the setting of a highly curable disease, outcomes such as lines of chemotherapy with the short- and long-term side effects and time to remission that affect quality of life must be considered.

CONCLUSION: Primary chemotherapy for PMGTN prior to referral to our specialty center was associated with increased need for additional lines of chemotherapy,

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resulting in a significantly prolonged time to remission.
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Molar pregnancy affects approximately 1 in 1,500 pregnancies in the Unites States.[1] Fortunately, the majority of molar pregnancies will resolve spontaneously, with normalization of the human chorionic gonadotropin (hCG) levels after evacuation of the pregnancy.[2] Postmolar gestational trophoblastic neoplasia (PMGTN) is diagnosed when the hCG does not spontaneously normalize following a molar gestation and additional treatment, such as chemotherapy or additional surgery, is required for treatment.[3] In the United States the incidence of PMGTN is estimated to be 18–29% following a complete molar pregnancy and 1–5% following a partial mole.[4,5] Fortunately, PMGTN is highly treatable with chemotherapy, with cure rates ranging from 80–100%.[6,7]

In the United States the American College of Obstetricians and Gynecologists (ACOG) released a practice bulletin with recommendations for following molar pregnancy and diagnosing PMGTN.[8] This document is intended for use by general obstetrician/gynecologists and, as such, encourages management of these patients in the community prior to referral into a specialty trophoblastic disease center. Prior data from our center demonstrated that women with PMGTN do not have a difference in clinical outcome whether they are referred to the New England Trophoblastic Disease Center (NETDC) after the diagnosis of molar pregnancy or at the time of persistence following the molar gestation.[9]

Data from other centers in the United States and abroad, however, indicate that women with gestational trophoblastic neoplasia (GTN) do have better clinical outcomes when managed by a specialty referral center.[10,11] Investigators at the John I. Brewer Trophoblastic Disease Center at Northwestern University in Chicago, Illinois, reported their outcomes of women with GTN treated with chemotherapy and demonstrated a lower rate of remission in women who had chemotherapy failure before referral (48% vs. 83%).[12] Though their survival rates improved in the 2008 update to this series (93%), the authors continued to show incorrect use of chemotherapy in the community prior to referral.[13]

Given the data from the Brewer Center demonstrating improved outcomes if a specialty center manages the entire GTN therapeutic course, the aim of this study was to investigate the timing of referral to the NETDC and determine if chemotherapy treatment of GTN prior to referral adversely affects a patient's clinical outcome. By understanding these patterns and associations, we hope to clarify appropriate timing for women with PMGTN to be referred to a specialty center, while maximizing care in the community and optimizing patient outcome.

Materials and Methods

With approval from the Institutional Review Board, the database of the NETDC was queried from January 1993 through December 2013 to find all women with PMGTN who had first-line chemotherapy failure. Sixty-five women met the inclusion criteria and formed the study population. Each patient had an antecedent molar pregnancy and met the International Federation of Gynecology and Obstetrics (FIGO) criteria for PMGTN: displayed an hCG plateau of ±10% over the course of at least 3 weeks, exhibited a rise of serum hCG >10% over the course of 2 weeks, or showed metastasis before hCG plateau or rise.[14] All patients underwent appropriate staging, including chest x-ray or computed tomography scan, baseline serum hCG, and pelvic ultrasound, and all were assigned a FIGO stage and FIGO/World Health Organization (WHO) risk score. Date of remission was defined as the first negative hCG value, though 3 weeks of negative hCG values were required for diagnosis of remission.

Two cohorts were created, dividing the study population by whether the patients received any chemotherapy prior to referral to the NETDC, and these groups were used for the primary analysis. A secondary analysis was performed using 3 cohorts: women referred with a diagnosis of molar pregnancy and diagnosed with PMGTN and treated after referral, women referred after diagnosis of PMGTN but before any chemotherapy, and women referred after receiving at least 1 line of chemotherapy with another provider.

The patients' charts were reviewed, and clinical and pathologic variables were extracted and recorded, including patient age and gestational age at the time of molar evacuation, histology of molar

pregnancy, hCG at molar evacuation and at the diagnosis of persistent disease, the dates of evacuation, persistence, and remission, FIGO stage, FIGO/WHO score, and lines of chemotherapy required for remission. Time to persistence (days) was defined as the time between molar evacuation and PMGTN diagnosis. Time to remission (days) was defined as the interval between PMGTN diagnosis and first nondetectable hCG value. Univariable and multivariable statistical tests were performed using logistic and linear regression as well as parametric and nonparametric testing as indicated. Time to remission analysis was performed utilizing the Kaplan-Meier method and compared using a log-rank test. Statistical tests were interpreted as significant if the alpha level was <0.05. STATA v14 (College Station, Texas) was utilized to perform all analyses.

Results

From January 1993 through December 2013, 429 women were evaluated by the NETDC for molar disease, of whom 171 women (40%) were diagnosed with PMGTN. Most women (62%) with PMGTN achieved remission with 1 line of chemotherapy; however, 65 women (38%) required at least 2 lines of chemotherapy for durable normalization of their hCG. These 65 women with PMGTN who experienced failure of first-line treatment made up the study cohort. These women were divided into 2 groups by whether or not they received any chemotherapy prior to evaluation by the NETDC. Forty-seven women (72%) received all treatment at the NETDC, and 18 women (28%) were treated prior to referral (Table I). There were no differences between these cohorts with regard to age at molar evacuation (31.2 vs. 30.0 years, $p=0.56$), hCG at molar evacuation (446,090 vs. 312,208 mIU/mL, $p=0.41$), gestational age at molar evacuation (10.1 vs. 8.7 weeks, $p=0.11$), or type of antecedent pregnancy (complete vs. partial mole, $p=0.75$). Time from molar evacuation to diagnosis of PMGTN was not different between the groups (39 vs. 45 days, $p=0.46$). A greater proportion of women were referred after first-line therapy in the second half of the time period of the study (2003–2013) as compared to the first 10 years (40% vs. 17%, $p=0.04$).

Several clinical features were different between the cohorts of women referred before or after first-line chemotherapy (Table I). Similar numbers of women referred after treatment had advanced (stage III or IV) FIGO stage (44% vs. 30% referred before chemotherapy, $p=0.26$). However, women with a high-risk FIGO/WHO prognostic risk score (defined as ≥7) were found only in the group referred after outside chemotherapy (33% vs. 0%, $p<0.001$). Additionally, women referred after chemotherapy had a significantly higher hCG at the time

Table I *Patient Characteristics Stratified by Referral Group*

	All chemotherapy after referral to NETDC	Referred after initial chemotherapy	p Value
No. of patients (n=65)	47	18	n/a
Age at molar evacuation (mean), yrs	31.2	30.0	0.56
hCG at molar evacuation (mean), mIU/mL	446,090	312,208	0.41
Gestational age at molar evacuation (mean), wks	10.1	8.7	0.11
Antecedent pregnancy			0.75
Complete mole	43	16	
Partial mole	4	2	
Time period			0.04
1993–2002	29 (83%)	6 (17%)	
2003–2013	18 (60%)	12 (40%)	
FIGO stage			0.26
Early stage (I and II)	33 (70%)	10 (56%)	
Late stage (III and IV)	14 (30%)	8 (44%)	
WHO risk score*			<0.001
<7	46 (100%)	12 (67%)	
≥7	0 (0%)	6 (33%)	
hCG at persistence (mean), mIU/mL	13,246	147,646	0.01
Days to persistence (median)	39	45	0.46

*WHO risk score missing for 1 patient.

persistence was diagnosed (147,646 IU/L vs. 13,246 IU/L, p=0.01). Women who were treated prior to referral to the NETDC required more lines of chemotherapy to achieve remission when compared to patients who received all treatment after consultation (50% received >2 lines of chemotherapy, vs. 15%, p=0.003) (Table II). Receiving chemotherapy prior to referral to the specialty center was also associated with a longer median time to remission (107 vs. 78 days, p=0.01) (Figure 1) (Table II).

Given the differences between the groups, multivariate analysis was performed controlling for patient age at molar evacuation, hCG at the diagnosis of persistence, and WHO score. Timing of referral to the NETDC remained significantly associated with requiring >2 lines of chemotherapy to achieve remission (p=0.04). Though no longer statistically significant, timing of referral was associated with a 46% reduction in the time to remission in the multivariate model (HR 0.54, 95% CI 0.27–1.07; p=0.08) when controlling for all factors listed above.

To assess the role of timing of referral further, the cohort of women who received all chemotherapy after referral to the NETDC was divided into the women who were referred with a diagnosis of molar pregnancy and were subsequently followed at the NETDC for a diagnosis of PMGTN (group 1, n=15) and those who already carried a diagnosis of PMGTN prior to referral (group 2, n=32). Analyzing these 2 groups along with the cohort of women who were treated for PMGTN prior to referral (group 3, n=18) demonstrated no difference between group 1 and group 2 with regard to needing >2 lines of chemotherapy to achieve remission, and both were statistically less likely to require >2 lines as compared with group 3 (p<0.001). Additionally, time to remission was similar between groups 1 and 2 and significantly shorter than time to remission in group 3 (p=0.04) (Figure 2).

Table II *Patient Outcomes*

	All chemotherapy after referral to NETDC	Referred after initial chemotherapy	p Value
Lines of chemotherapy to remission			0.003
2	40	9	
>2	7	9	
Days to remission after persistence (median)	78	107	0.01

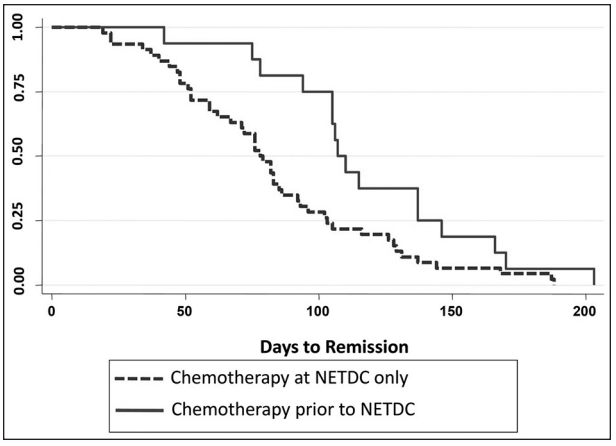

Figure 1 Time from diagnosis of PMGTN to remission stratified by timing of referral to NETDC. Women who received all their chemotherapy at the NETDC had a shorter time to remission as compared to women who received cycles of chemotherapy prior to referral to the NETDC (p<0.01).

Discussion

This study covers a 21-year experience in a specialty trophoblastic disease center in the northeastern United States. In this population of 65 women who experienced failure of first-line chemotherapy for PMGTN, there was an increased likelihood of success of second-line chemotherapy and a decreased time to achieve remission in the cohort of women who received all treatment after referral to the NETDC. The women treated elsewhere prior to referral had some clinical characteristics associated with worse GTN outcomes, including higher WHO score and higher hCG at diagnosis of PMGTN; these findings likely reflect referral bias in this population. Importantly, controlling for these different factors between the referral cohorts did not negate the independent association of timing of referral on lines of chemotherapy needed to achieve remission.

These data are consistent with those from other centers. Hoekstra et al from the Brewer Center demonstrated, in an analysis of 408 women with GTN, that prior unsuccessful chemotherapy before referral to the specialty center was significantly associated with resistance to further treatment.[15] In Brazil an analysis of women with PMGTN demonstrated that women followed in the Botucatu Trophoblastic Disease Center had a significantly lower risk of requiring multiagent chemotherapy to achieve remission when compared to women managed at noncentralized centers prior to refer-

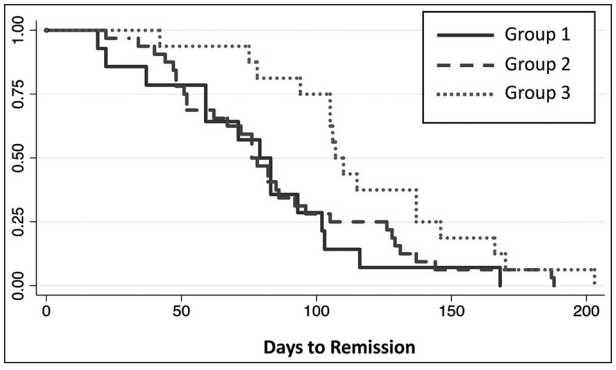

Figure 2 Time from diagnosis of PMGTN to remission by timing of referral to NETDC. While no difference in time to remission was observed among women referred to the NETDC with molar pregnancy (Group 1) or untreated PMGTN (Group 2), those women referred after first-line therapy manifested a longer time to remission ($p<0.001$).

ral.[11] Several authors in various countries have now advocated for the management of GTN in specialty centers to maximize patient outcomes in this rare disease.[7,11,13,16,17]

In contrast, we observed in a prior series that there was no difference in outcomes of PMGTN by timing of referral.[9] That study assessed outcomes by referral with molar pregnancy versus PMGTN and suggested that general gynecologists in the community can monitor molar pregnancies up to the point of remission or GTN without compromising clinical outcomes. It is possible that the firm ACOG guidelines around the follow-up care for patients with molar pregnancy in the United States ensure that these women receive appropriate and timely care in the community and therefore do not have different outcomes. Our prior study differs from this current investigation that examines referral patterns before and after chemotherapy has been administered for established GTN. These data echo the studies from Brazil and Northwestern highlighting inferior outcomes if GTN care is not centralized in an established trophoblastic center. These data highlight that chemotherapy for GTN can present therapeutic challenges to clinicians who uncommonly manage this disease, and this key difference is a likely explanation for the differing results seen between our two studies.

Though these women, as in the Brazilian and Northwestern series, were ultimately treated in a specialty center and achieved remission, they required more chemotherapy and more time in treatment.[15] These outcomes could be associated with increased anxiety and decreased quality of life for patients with PMGTN and their families.[18] In the setting of a highly curable disease, outcomes such as lines of chemotherapy with the short- and long-term side effects and time to remission that affect quality of life must be considered. Women with PMGTN tend to be otherwise young and healthy, and so societal considerations such as cost, time out of work, and time to subsequent pregnancy also can play a role in treatment decisions. If earlier referral to a specialty center could allow women to achieve an earlier remission with less treatment, it also may be cost-effective to refer. Cost and quality of life should be further evaluated in a prospective trial.

This study is limited by its retrospective nature, which inherently did not allow for standardization of the management of these patients at the NETDC and which can be biased by clinical and demographic information that is unavailable from the records. Inherent in the study design is the challenge of understanding the granular doses and schedules of chemotherapy administered outside of the referral center which was unavailable in the majority of cases. Attempts were made to improve this by accessing only patients treated since the introduction of an electronic medical record, allowing for better extraction of data and more uniform charting. More importantly, the intrinsic nature of a referral center means that every patient receiving care at the NETDC was referred to the center at some point in her care. This introduces a referral bias in a country like the United States, where there are not strict guidelines for when and whom to send to a specialty center. Referral bias may account for some of the results seen in this study, although this was limited by inclusion of only women refractory to first-line chemotherapy, as women who went into remission with initial treatment in the community presumably would not be referred and were therefore not in this study. Additionally, multivariate analysis accounting for the clinical differences seen between the referral populations did not erase the clinical benefit associated with all chemotherapy treatment after referral to the NETDC.

In conclusion, this longitudinal experience at a specialty referral trophoblastic disease center in the northeastern United States demonstrates that women with PMGTN who were treated with chemotherapy prior to referral to the NETDC required

more lines of chemotherapy and a longer time to achieve remission than did women who had all treatment after referral. Additionally, these data also demonstrated a trend toward more treatment outside of specialty centers prior to referral in the latter half of this data collection period, which is contrary to the best practice pattern suggested by this study. These data, in combination with other studies in the literature and our prior series assessing referral with molar pregnancy, highlight the importance of consultation with a specialist in trophoblastic disease prior to initiation of chemotherapy for PMGTN in the United States.

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