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Continued hCG surveillance following chemotherapy for gestational trophoblastic neoplasia: When is enough enough?

Gestational trophoblastic neoplasia (GTN) has the highest rate of long-term cure among all gynecologic malignancies. Overall survival rates stratified by International Federation of Gynecology and Obstetrics (FIGO) prognostic risk score approach 100% for low-risk disease (score <7) and exceed 90% even for high-risk disease (scores ≥7) [1]. This stems from high rates of primary remission with chemotherapy as well as very high salvage rates from second- and third-line regimens. Remission in GTN is defined by human chorionic gonadotropin (hCG) levels falling below the lower limit of detection of the employed reference assay. Currently, the National Comprehensive Cancer Network (NCCN) recommends post-treatment surveillance for GTN with one year of monthly serum hCG monitoring [2]. However, relapses can occur beyond the one-year mark, raising the question of whether longer term surveillance is warranted.

In this issue of *Gynecologic Oncology*, Balachandran and colleagues investigate the risk of GTN relapse using a population-based cohort study from the United Kingdom [3]. With regards to post-GTN hCG surveillance, the policy at the reporting centers has been for indefinite hCG monitoring for all women treated for GTN. The authors report the risk of relapse was 4.4% for low-risk patients (154/3507) and 6.3% (44/694) for high-risk patients. In both risk cohorts, more than 75% of these relapses occurred within the first year, making the overall risk of relapse beyond one year 1.2% of low-risk patients (42/3507) and 0.9% (6/694) of high-risk patients. No relapses were detected after seven years of monitoring. From these results, the authors recommend ten years of monitoring. Notably, this would extend post-treatment monitoring for GTN beyond the current Society of Gynecologic Oncology recommendations for other gynecologic tumors [4]. With the risk of recurrence of approximately 1% after the first year, one could reasonably invoke the law of diminishing returns. Depending upon the risk tolerance of the patient and the provider, a 1% relapse risk may be low enough.

The strengths of this study include the sample size and the use of centralized hCG testing. For almost fifty years, all patients in the UK with GTN have been treated at either Charing Cross Hospital in London or Weston Park Hospital in Sheffield [5,6]. This has created a rich clinical experience from which the centers have been able to perform many of the seminal studies in the treatment of this disease. When combined with the nationalized healthcare system of the UK, this makes the current report essentially a calculation of the cumulative lifetime risk of GTN relapse at the population level. Given the nationwide referral base, there is very little room for ascertainment bias in the data. Moreover, hCG monitoring in the UK is done centrally at the reference centers. Unlike in the United States, where hCG monitoring is usually serum-based and performed locally, in the UK hCG surveillance is done by urine testing, with samples mailed to the reference centers for analysis. Notably, the urine assay utilized is a proprietary high sensitivity radioimmunoassay, not the typical commercial hCG urine assay available at most centers. Other centers considering urine monitoring should keep this in mind when interpreting these results as conventional urine hCG assays are less sensitive to low level hCG levels than serum assays.

A major challenge in considering this study is the definition of relapse. The authors do not provide a definition of relapse beyond a rise in hCG values after the cessation of chemotherapy. It is not clear from the current report whether a single elevated hCG value would be sufficient to diagnose relapse or whether other criteria are used. Our only clue is the date of relapse being defined as the commencement of chemotherapy. In this study, the authors also did not adjust the relapse rates for the number of patients who could physiologically become pregnant (for example, had not had a hysterectomy). Presumably, many of the patients in this study desired fertility and did not continue contraception beyond the first year of hCG surveillance. Among fertile couples, more than 20% of pregnancies spontaneously abort before a pregnancy is detected clinically [7]. As the recurrence rate for GTN is 1% after the first year, it becomes increasingly more likely that an elevated hCG after the first year is an unrecognized intercurrent gestation rather than a true GTN relapse. [8]. Distinguishing GTN recurrence therefore becomes particularly challenging after the first year of follow-up. In addition, it is unclear what percentage of patients were asymptomatic at the time relapse was diagnosed. Patients should also have an hCG level checked during evaluation for abnormal uterine bleeding or for unexpected infertility. Limiting the current report to relapses diagnosed in completely asymptomatic women with the ability to conceive (i.e. no hysterectomy for their GTN) might change the occult relapse rate thus making prolonged hCG follow-up less useful .

Another limitation to the work is that relapse rates over time were not correlated to updates in clinical practice. Recent decades have seen increased use of consolidation chemotherapy, which reduces relapse rates [9]. Increasing the number of consolidation chemotherapy cycles from two to three courses further reduces the relapse rate from 8.3% to 4% [10].

Finally, extended hCG monitoring is likely to lead to some false positive tests for relapse among older patients. Patients who develop complete molar pregnancies over age 40 are more likely to develop GTN [11,12]. Extended hCG monitoring in these patients will follow them into perimenopause. A common cause of a “false positive” hCG test is pituitary hCG, which is most likely to occur in perimenopausal

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women [13,14]. In post-menopausal women, the prevalence of detectable hCG levels up to 14 mIU/mL is 8% [15]. While pituitary hCG can be distinguished from GTN by placing a patient on oral contraceptive pills to suppress pituitary hCG production, women in their 40s and 50s are less likely to use oral contraceptives due to the risks of thromboembolic disease. Any protocol for extended hCG monitoring post-GTN should incorporate steps for evaluating other causes for hCG elevation.

In summary, this study provides valuable information in counseling patients regarding the long-term risks of GTN relapse following chemotherapy. Beyond the monetary expense of prolonged hCG monitoring, the psychological burden is significant for patients and their partners with both expressing a fear of disease recurrence for years following therapy [16]. With these data, most patients should feel reassured that the chances of relapse beyond the first year are about 1% and feel comfortable to attempt another conception if desired. After three years of follow-up hCG monitoring, the risk of relapse in low-risk GTN is 6/3507 or 1/585 (0.2%) and in high-risk GTN is 2/694 or 1/347 (0.3%). However, two different individuals, both comparably knowledgeable, concerned, and compassionate, looking at the same data, may draw different conclusions. If the risk for relapse for low-risk and high-risk GTN after three years of follow-up is only 0.2% and 0.3%, respectively, should one be concerned that the monitoring is not adequate? Is zero percent tolerance of missing relapse the most appropriate goal?

While agreement on what is the most appropriate goal to detect relapse will be challenging, this manuscript nonetheless provides important data to guide shared decision making. Regardless of how one interprets the benefits of extended hCG monitoring, the possibility of late relapse should be considered in patients with abnormal uterine bleeding, difficulty becoming pregnant, or in the case of an incidental finding of an elevated hCG. However, with increasing time from GTN treatment, other causes of abnormal hCG elevation other than relapsed GTN, such as another gestation or pituitary hCG, become more likely. Prolonging the follow-up surveillance beyond a year of monthly hCG needs to be considered carefully, weighing the risk of late recurrence against delaying future pregnancy and the psychosocial impact of maintaining the "disease state". As the risk of late recurrence becomes diminishingly small, one must ask when the balance should tip in favor of discontinuing monitoring. Ultimately, the decision of how long to monitor hCG post-chemotherapy for GTN will depend on the risk tolerance of the patient and provider. Based upon the data presented in this article, we would not recommend any changes in NCCN guidelines of one year of monthly serum hCG monitoring in asymptomatic patients. However, if following completion of hCG monitoring, patients develop new symptoms, such as abnormal bleeding, then the possibility of recurrence should be considered, and an hCG level should be obtained.

Conflict of Interest Statement

The authors do not have any conflicts to disclose.

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Author contributions

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