Gestational Trophoblastic Disease
Opportunities for a National Registry Collaboration

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Objective: In rare entities such as gestational trophoblastic disease (GTD), only multi-institutional registries can gather significant number of patients to build up valuable clinical databases. No Canada-wide GTD registry currently exists. We conducted a survey among members of the Canadian Society of Gynecologic Oncology (GOC) to investigate their interest in a pan-Canadian GTD registry. We also took the opportunity to explore their management of GTD.

Methods: An electronic survey was conducted. The target group was the entire GOC Canadian Membership. The survey consisted of 25 questions.

Results: The survey participation rate was 39% (67/171). Seventy-six percent of responders treat patients with molar pregnancy or gestational trophoblastic neoplasia (GTN), and the majority treat only 5 or less cases of molar pregnancy and 5 or less cases of GTN per year. In cases of low-risk GTN, 80% of responders use generally recommended single-agent chemotherapy regimens. In cases of high-risk GTN, 76% use generally recommended multiagent chemotherapy regimens. Most respondents do not submit either molar pregnancy or GTN patients to any formal registry, although the vast majority (92%) would do so if they had access to a registry, given that most believe that a registry can or probably can help patients with GTD. Responders indicated that the jurisdiction of such a registry should be national (59%), provincial (25%), and regional (11%).

Conclusions: Despite some variation, responders were generally knowledgeable about contemporary management issues. Canadian Society of Gynecologic Oncology members acknowledge generally low exposure to GTD patients in Canada and support the creation of a national GTD registry to facilitate optimal patient care, education, and research.

Key Words: Gestational trophoblastic disease, Gestational trophoblastic neoplasia, Registry, Database, Management

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As demonstrated in other cancer types, the management and outcomes for patients with gestational trophoblastic disease (GTD) have improved with the creation of referral centers.[1] Such centers have developed in the last years in many European,[2,3] Asian,[4–7] and South-American countries.[8–10] Such a referral center has also been created in Canada within the province of Québec in 2009 (Québec Trophoblastic Disease Registry/ Réseau des Maladies Trophoblastiques du Québec-RMTQ).[11]

Clinical databases have become critical tools to facilitate optimal patient care, education, and research. However, in the case of rare diseases such as GTD, single institutional databases are insufficient and only multi-institutional (ideally national or multinational) registries can gather significant numbers of patients for these purposes. The RMTQ fulfills this requirement as a registry for referred patients from Quebec, and at least 1 other clinical GTD database is known to exist in Canada. However, no Canada-wide GTD registry currently exists.

We conducted a survey (Supplemental Digital Content 1, http://links.lww.com/IGC/A397) among members of the Canadian Society of Gynecologic Oncology (GOC) to investigate their interest for a pan-Canadian GTD registry. We also took the opportunity to explore their management of GTD.

METHODS

An electronic survey was conducted using Survey Monkey during 5 weeks at the end of 2013. The target group was the entire GOC Canadian Membership who were recruited through their professional e-mail address. Two e-mail reminders were sent out during that period. The survey consisted of 25 questions regarding demographic characteristics of the participants, general information on their practices related to GTD, including pathology, treatment, follow-up, and specific questions focused on issues surrounding registration (see appended Survey). Answers were determined through selection of one of the provided choices for most questions; however, text boxes were provided for participants to provide "other" answer in many questions. Only the information most relevant to the present article is described in detail and discussed here.

RESULTS

The survey participation rate was 39% (67/171). Not all responders responded to every question, leaving varied denominators for results reported later.

Most responders (45/62) indicated that they are gynecologic oncologists. With respect to their current practices, 51 (76%) of 67 responders treat patients with molar pregnancy or GTN. Thirty-seven (80%) of 46 treat 5 cases or less of molar pregnancy per year; 36 (80%) of 45 treat 5 cases or less of gestational trophoblastic neoplasia (GTN) per year (Fig. 1).

Of 49 responders, 48 reported having most of their GTD cases referred from gynecologists and 1 reported having most cases referred from other gynecologists oncologists.

Of 47 respondents, 34 (72%) do not submit molar pregnancy patients to a formal registry and 31 (66%) similarly do not register GTN patients. Of 63 respondents, 58 (92%) believe a registry can (40/63) or probably can (18/63) help patients with GTD. Of 63 respondents, 58 (92%) would register

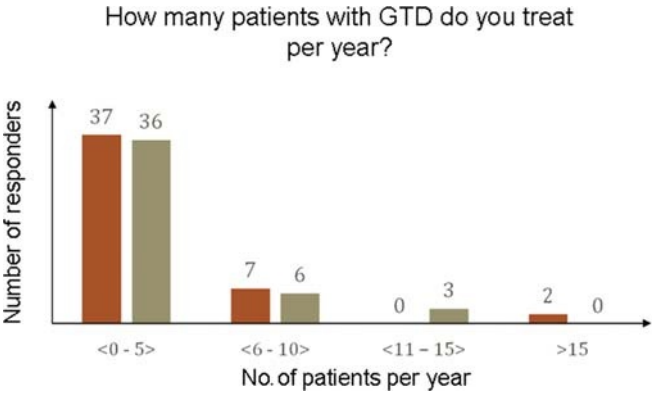

FIGURE 1. Survey responses from GOC members regarding the frequency of GTD patients managed per year. A total of 46 responded to this question for molar pregnancies, and a total of 45 responded to this question for GTN. Orange, molar pregnancies; green, GTN.

patients if they had access to a registry (Fig. 2). Responders indicated that the jurisdiction of such a registry should be national (36/61, 59%), provincial (15/61, 25%), and regional (7/61, 11%).

Of 47 responders, 36 (77%) have pathology reviewed for all cases of GTD, but 11 (23%) do not. For those who routinely review pathology, 18 (58%) of 31 use p57 and 18 (58%) of 31 use ploidy as part of the pathology review process.

Of 49 responders, 45 (92%) use the International Federation of Gynecology and Obstetrics (FIGO)/World Health Organization (WHO) 2000 score during management of all GTN patients, and 36 (73%) of 49 use the FIGO/WHO 2000 staging system for all their GTN patients.

Responders indicated that their practices regarding duration of follow-up required after a suction Dilation and Curettage for a molar pregnancy is based on the following: time to negative hCG (26/46, 57%), pathologic diagnosis (partial vs complete mole; 14/46, 30%), and other factors (6/46, 13%; including a combination of the previous criteria; 6–12 months, and patients' desire to pursue pregnancy). Similarly, the duration of follow-up after treatment for GTN was based on various factors including WHO risk category; for low-risk GTN (WHO score $\leq$6), 38 of 42 responders follow patients for 6 to 12 months after achieving a negative hCG, 4 of 42 follow longer; for high-risk GTN (WHO score $\geq$7), 38 of 45 follow for 2 or more years, 6 follow for 1 year, and 1 respondent based follow-up on the patient's fertility wishes.

In cases of low-risk GTN, 35 (80%) of 44 respondents use generally recommended single-agent chemotherapy regimens including the following: pulsed actinomycin-D (16/44), intramuscular methotrexate weekly (15/44); 5- to 8-day regimens of intramuscular methotrexate with folic acid (4/44); others indicated using methotrexate alternating with actinomycin-D (8/44); and intravenous Methotrexate weekly (1/44).

In cases of high-risk GTN, 32 (76%) of 42 respondents use generally recommended multiagent chemotherapy regimens (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine or etoposide, methotrexate, and dactinomycin with etoposide and cisplatin); 8 of 42 use some other multiagent

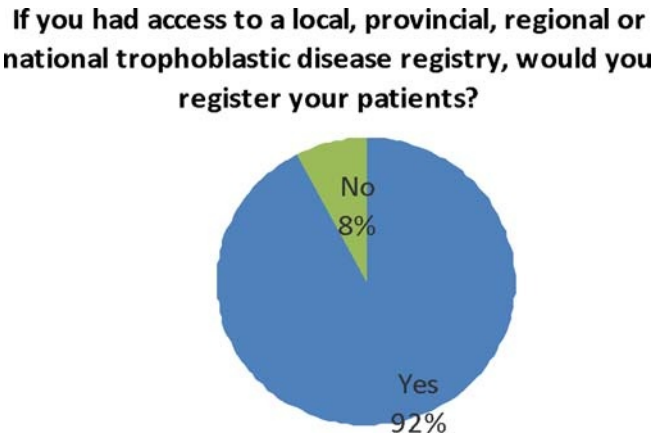

FIGURE 2. Survey responses from GOC members regarding commitment to use a GTD registry if one existed. Of 63 responders, 58 (92%) would register their patients.

chemotherapy regimen (methotrexate, dactinomycine and cyclophosphamide, etoposide, methotrexate, actinomycin D, Bleomycin, Etoposide, cisplatin, cisplatin + etoposide); 2 of 42 use single-agent chemotherapy (methotrexate or actinomycin-D). In cases of GTN with brain metastases, 19 (41.3%) of 46 respondents use high-dose EMA-CO without (17/46) or with (2/46) intrathecal methotrexate; 19 (41.3%) of 46 use whole-brain radiotherapy concurrent with chemotherapy; otherwise, 5 have never treated such patients; 2 "individualize" treatment; and 1 uses high-dose EMA-EP.

DISCUSSION

This survey of GOC members examined their perspectives on a potential pan-Canadian GTD registry and explored their practices regarding GTD management. The overall response rate was modest (37%), and we believe that it is most likely that those GOC members interested in GTD and/or treating patients with GTD were also interested in and responded to this survey. Interestingly, only 76% of respondents to our survey indicated that they actually treat patients with GTD/GTN, which may also contribute to the modest response rate seen to our survey.

In Canada, patients with GTN are referred to gynecologic oncologists universally from gynecologists, and in our experience, it is uncommon in the Canadian health system for gynecologists to refer GTD/GTN cases to a medical oncologist, most of whom are not GOC members. Therefore, we believe that this study captures a representative picture of GTD/GTN practices and management in Canada.

In addition to documenting that not all GOC members treat patients with GTD, this survey also confirms a low level of exposure to trophoblastic disease among GOC members and that most responders (80%) treat 5 affected patients or less per year (Fig. 1). In fact, a significant proportion (5/46) acknowledges never having encountered a patient with brain metastases. In such complex cases, patients treated by physicians experienced in the management of trophoblastic disease have better survival.[12] These data highlights potential benefit to patient management through creating a pan-Canadian registry linked with experts in GTD management based at referral centers.

Twenty-three percent of responders do not use pathologic review for all GTD cases. In the literature, complete mole is very generally accurately diagnosed by community pathologists.[13] On the contrary, expert pathologic review of partial molar pregnancy changes the diagnosis in 36% of cases, with consequent change in management such as extended follow-up because of a higher risk of associated trophoblastic cancer (change from partial mole to complete mole in 28% of cases), or on the contrary avoidance of unnecessary follow-up and anxiety (change to nonmolar pregnancy with hydropic villi in 7% of cases).[13] Almost half of responders to our survey do not use p57 and/or ploidy studies during pathologic evaluation of GTD cases, both of which are recognized to be helpful in making the right pathologic diagnosis.[14,15] Based on our survey, registration of all GTD cases and management through associated referral centers in Canada would also improve patient care through facilitating routine expert pathologic review.

Responders to our survey were generally knowledgeable about contemporary management issues including duration of follow-up after GTD, the utility of FIGO scoring/WHO staging and the appropriate treatment of patients with low- and high-risk GTN. However, there are significant variations in the management of GTD among Canadian GOC members, which may simply reflect the paucity of high-quality data.[1] Evidence-based practices are more difficult to develop in rare tumors such as GTD. This makes registries particularly important, allowing the collection and analysis of experienced-based data.

Based on the previous considerations, in addition to the benefits to research and education, we believe a pan-Canadian GTD registry is an important next step toward improved outcomes for affected women in Canada. Although currently most responders do not register patients with GTD, almost all responders agreed that a registry may help patients with GTD and indicate that they would register such patients if a registry were available. Most responders consider such a registry should be national in scope, likely reflecting the rarity of these cases to facilitate more uniform management and data collection across the country.

CONCLUSIONS

Gestational trophoblastic diseases are rare entities best managed in a defined system of care, which in many jurisdictions, include mandatory registration of cases and management at expert referral centres. To date, in Canada, GTD management has been largely decentralized and based on local expertise. Within this survey, GOC members acknowledge generally low exposure to GTD patients in Canada and support the creation of a national GTD registry.

In our view, from the Canadian perspective, a realistic proposition for structuring GTD care would be the creation of a national registry including a comprehensive database for epidemiology, education, and research, in addition to several referral centers to facilitate routine pathology review and to help with management of complex cases. The first step

toward this realization has been the creation of a web forum to discuss complex GTD cases on the GOC Web site, through the GOC Trophoblastic Disease Community of Practice. Currently, a national web-based database is being elaborated to facilitate registration of all GTD cases; it will be important that all these pathologies be routinely subjected to expert review. It is hoped that the upcoming International Society for the Study of Trophoblastic Disease meeting in Toronto, Canada (2019), may draw the attention of GOC members and Canadian gynecologists to the need to develop and implement a formal GTD system in Canada, based on the pervious considerations, to improve the management of Canadian women with trophoblastic disease.

REFERENCES

1. Seckl MJ, Sebire NJ, Fisher RA, et al. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24:vi39–vi50.
2. Golfier F, Raudrant D, Frappart L, et al. First epidemiological data from the French Trophoblastic Disease Reference Center. *Am J Obstet Gynecol*. 2007;196:172.e1–172.e5.
3. Van der Houwen C, Rietbroek RC, Lok CA, et al. Feasibility of central co-ordinated EMA/CO for gestational trophoblastic disease in the Netherlands. *BJOG*. 2004;111:143–147.
4. Kim SJ, Bae SN, Kim JH, et al. Effects of multiagent chemotherapy and independent risk factors in the treatment of high-risk GTT—25 years experiences of KRI-TRD. *Int J Gynaecol Obstet*. 1998;60(suppl 1):S85–S96.
5. Chu MM, Ma Y, Tse KY, et al. Cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, and vincristine in the treatment of gestational trophoblastic neoplasia. *Int J Gynecol Cancer*. 2015;25:498–503.
6. Wang KL, Yang YC, Wang TY, et al. Treatment of gestational trophoblastic neoplasia according to the FIGO 2000 staging and scoring system: a 20 years' experience. *Acta Obstet Gynecol Scand*. 2009;88:204–208.
7. Tse KY, Chan KK, Tam KF, et al. 20-year experience of managing profuse bleeding in gestational trophoblastic disease. *J Reprod Med*. 2007;52:397–401.
8. Dantas PR, Maestá I, Cortés-Charry R, et al. Influence of hydatidiform mole follow-up setting on postmolar gestational trophoblastic neoplasia outcomes: a cohort study. *J Reprod Med*. 2012;57:305–309.
9. Bianconi MI, Otero S, Moscheni O, et al. Gestational trophoblastic disease: a 21-year review of the clinical experience at an Argentinean public hospital. *J Reprod Med*. 2012;57:341–349.
10. Braga A, Uberti EM, Fajardo Mdo C, et al. Epidemiological report on the treatment of patients with gestational trophoblastic disease in 10 Brazilian referral centers: results after 12 years since International FIGO 2000 Consensus. *J Reprod Med*. 2014;59:241–247.
11. Sauthier P, Breguet M, Rozenholc A, et al. Quebec Trophoblastic Disease Registry: how to make an easy-to-use dynamic database. *Int J Gynecol Cancer*. 2015;25:729–733.
12. Kohorn EI. Worldwide survey of the results of treating gestational trophoblastic disease. *J Reprod Med*. 2014;59:145–153.
13. Golfier F, Clerc J, Hajri T, et al. Contribution of referent pathologists to the quality of trophoblastic diseases diagnosis. *Hum Reprod*. 2011;26:2651–2657.
14. Ngan HY, Seckl MJ, Berkowitz RS, et al. Update on the diagnosis and management of gestational trophoblastic disease. *Int J Gynaecol Obstet*. 2015;131(suppl 2):S123–S126.
15. Mangili G, Lorusso D, Brown J, et al. Trophoblastic disease review for diagnosis and management: a joint report from the International Society for the Study of Trophoblastic Disease, European Organisation for the Treatment of Trophoblastic Disease, and the Gynecologic Cancer InterGroup. *Int J Gynecol Cancer*. 2014;24(9 suppl 3):S109–S116.

