Neuro-Oncology
21(12), 1490–1492, 2019 | doi:10.1093/neuonc/noz188 | Advance Access date 8 October 2019

"Not all that glitters is gold": insights from the Far East and how to solve a conundrum

Nicholas G. Gottardo and Ute Bartels

Department of Paediatric and Adolescent Oncology/ Haematology, Perth Children's Hospital, Nedlands, Western Australia, Australia (N.G.G.); Brain Tumour Research Programme, Telethon Kids Institute, Nedlands, Western Australia, Australia (N.G.G.); School of Medicine, Pediatrics, The University of Western Australia, Perth, Western Australia, Australia (N.G.G); Paediatric Brain Tumour Program, The Hospital for Sick Children, Toronto, Ontario, Canada (U.B.); University of Toronto, Toronto, Ontario, Canada (U.B.)

Corresponding Author: Nicholas G. Gottardo, Department of Paediatric and Adolescent Oncology / Haematology, Perth Children's Hospital, Nedlands WA 6009, Australia (nick.gottardo@health.wa.gov. au).

See the article by Takami et al. in this issue, pp. 1552–1564.

Takami and colleagues[1] report on the clinical, histopathological, and molecular features of central nervous system (CNS) germ cell tumors (GCTs). They conducted a retrospective series of 190 cases classified as primary GCTs, based on a central review from the *I*ntracranial Germ Cell Tumor (iGCT) Genome Analysis Consortium. Their goal was to address outstanding issues in the classification and clinical management of these tumors. The authors need to be commended on CNS GCT tissue collection and implementation of the iGCT Genome Analysis Consortium. However, the retrospective nature and the lack of homogeneously collected clinical data such as staging results and tumor marker and heterogeneous treatments limit some of their conclusions. In Europe and North America (the West), CNS GCTs account for 3% of all brain tumors, and their peak incidence is in the second decade of life, with a marked predilection for males. In contrast, in Japan and Far East Asia, these tumors make up 9–15% of all tumors, making them the second most commonly diagnosed brain tumor after gliomas. This marked geographical variation in incidence of GCTs and the different diagnostic approaches adopted in Japan (spearheaded by neurosurgeons and upfront tumor resection) present opportunities for the West to gain greater insights into this "mixed bag" group of tumors. However, it is possible or even likely that GCTs from patients from the Far East are biologically distinct from tumors from their Western counterparts.

In the West, the diagnosis of intracranial germinomas is based on characteristic tumor location using imaging and tumor marker patterns. Germinomas do not secrete alpha-fetoprotein (AFP) and may secrete low levels of beta human chorionic gonadotropin (β-hCG) (<50–100 IU/L), detected in the serum and/or CSF. The exact β-hCG threshold, however, remains to be determined.[2] Biopsy is required in marker-negative tumors.

Nongerminomatous germ cell tumors (NGGCTs) are a highly heterogeneous group of tumors, comprising yolk sac tumors (YSTs), embryonal carcinoma (EC), choriocarcinoma (ChC), immature teratoma with or without malignant components, and mixed malignant tumors in a variety of combinations, frequently with components of mature teratoma or germinoma. Classically, YSTs secrete only AFP, while ChC secretes only β-hCG, and EC may secrete both β-hCG and AFP.[3] Based on these characteristics, in North America and Europe, AFP elevations >10–25 ng/mL and/or β-hCG elevations >50–100 IU/L in the serum and/or CSF are sufficient for a diagnosis of NGGCT, and no biopsy is required before starting treatment.[2] Resection is reserved for residual tumors after completion of chemotherapy and prior to the start of radiotherapy, where the presence of residual tumor is associated with an inferior prognosis.[4]

Takami and colleagues' report highlights several important clinical and biological aspects:

Firstly, overall survival (OS) in germinoma with or without metastasis is excellent when treated with a combined chemoradiotherapy approach (Table 1). Of note, 8 patients with histopathologically confirmed germinoma demonstrated elevated tumor markers, above 25 ng/mL for AFP ($n = 4$) and/or above 50 IU/L for β-hCG ($n = 5$), respectively. This dismal progression-free survival (PFS) suggests that those patients were treated according to their histopathological diagnosis, and the authors underscore that tumor markers indeed need to be integrated into diagnosis and treatment. Sadly, this study was unable to identify a β-hCG threshold in serum or CSF to better distinguish germinoma with a syncytiotrophoblastic component from β-hCG producing NGGCTs, due to the lack of consistently collected serum/CSF marker at diagnosis. Thirty-four of 35 bifocal tumors were biopsy-proven germinomas and all

© The Author(s) 2019. Published by Oxford University Press on behalf of the Society for Neuro-Oncology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

but 2 were tumor marker negative. The one exception was a bifocal yolk sac tumor with exceedingly high AFP levels. Hence, this patient's treatment—even in the presence of a biopsy-proven germinoma—would have prompted appropriate NGGCT treatment. With this important finding in mind, the question now arises whether the risk of a biopsy in bifocal tumors is still appropriate in the presence of classical radiological and clinical features and in the absence of a biological prospective trial.

Secondly, compared with pure germinomas, NGGCTs have an inferior prognosis, as they are less radiosensitive (Table 2). One of the most notable findings was the presence of marker-positive germinomas (elevated AFP and/or moderately to severely elevated β-hCG) in 18.2% (8/44) of cases and 6.1% (2/33) of marker-negative NGGCT cases, highlighting that "not all that glitters is gold". This issue exposes the challenges of designing and running clinical trials in such rare and heterogeneous tumors, as a small number of erroneously diagnosed tumors have the potential of wrongly informing the trial. For example, a patient with marker-positive germinoma enrolled on an NGGCT trial could be overtreated and artificially raise survival rates. Conversely, a therapy reduction trial may fail due to a random overrepresentation of very high risk NGGCT. In the recently closed Children's Oncology Group (COG) study,[5] the efficacy of reduced dose and field radiation therapy (to whole ventricular irradiation with a boost to the tumor bed) was tested for non-metastatic patients who achieved a complete or partial response to the same chemotherapy as in the COG ACNS0122 trial.[14] The 3-year PFS and OS and standard error values were 87.8% ± 4.04% and 92.4% ± 3.3%. Eight of 66 patients progressed, and all patients had a component of spinal relapse.[5] These outcomes differed from the ACNS0122 study, where the majority of failures for non-metastatic NGGCTs were local. From these observations, one could conclude that the failure pattern is simply a reflection of the removal of craniospinal irradiation (CSI). However, the very small numbers of relapsed patients involved and the inclusion of differing proportions of patients with biologically distinct tumors is also plausible.

Thirdly, in the absence of prospective trials and consistent with the recommendation from the Delphi consensus,[2] if tissue is collected (upfront or after completion of chemotherapy) it is essential to homogeneously collect clinical data, to evaluate correlation between biology and outcome.

Finally, it is of note that novel drugs have not influenced treatment or the survival rates for GCT patients. For NGGCT patients, survival rates have plateaued, indicating that conventional therapy has achieved its full potential. Germinoma survivors still face lifelong treatment-related cognitive and endocrine side effects, due to the inability to dismiss radiation from treatment regimens. A previous report from the same group has revealed that germinomas and NGGCTs (including testicular GCTs) showed similar mutational profiles, suggesting a common molecular pathogenesis.[6] To date, however, studies using imatinib or dasatinb as novel therapeutic agents in progressive or relapsed GCT patients with inhibition of the Kit/Ras/Raf/mitogen-activated protein kinase (MAPK) and/or the Akt1/phosphatidylinositol-3 kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway have yielded disappointing results.[7,8] Using array-comparative genomic hybridization and either whole-exome or targeted sequencing, Takami and colleagues[1] undertook molecular analyses on 123 and 74 of the 190 cases (74 were analyzed for both), respectively. These relatively limited

Table 1 Survival of CNS germinoma according to different treatment groups

Treatment Group	5-y EFS	5-y OS
SIOP-GCT-96 results ($n = 235$)[9]	97%# / 88%$	95%#/ 96%$
SFOP experience ($n = 60$)[10]	84%	98%
Japanese GCT study group ($n = 228$)[11]	87%	98%^
CHLA experience ($n = 19$)[12]	89%*	100%*
Sick Kids experience ($n = 24$)[13]	96%**	100%
iGCT Consortium ($n = 96$)[1]	87%**	98.6%

*3-year event-free survival (EFS) and overall survival (OS).
**5-year progression free survival (PFS).
For CSI alone.
$ For focal radiotherapy and chemotherapy.
CHLA, Children's Hospital Los Angeles; NR, Not Reported; SFOP, French Society of Pediatric Oncology; SIOP, International Society of Pediatric Oncology.
^ Refers to a cohort of 123 patients, as described by the authors.

Table 2 Survival and relapse pattern of CNS NGGCT according to different treatment groups

Treatment Group	5-y EFS	5-y OS	Type of Relapse			
			Local	Distant	Combined	Marker Alone
COG ACNS0122 ($n = 102$)[14]	84 ± 4%	93 ± 3%	9	4	0	2
SIOP-GCT-96 ($n = 116$ localized [$n = 33$ metastatic])[4]	72 ± 4% / [68 ± 9%]	82 ± 4% / [75 ± 8%]	14[5]	7[1]	6[3]	0
iGCT Consortium ($n = 40$)[1]	79.5 ± 20.6%	76.1 ± 24.0%	NA	NA	NA	NA
ACNS1123[5] ($n = 66$)	87.8 ± 4.04%*	92.4 ± 3.3%*	0	6	2	0

EFS = event-free survival; SIOP = International Society of Pediatric Oncology.
*3-year progression free survival (PFS) and overall survival (OS).
**5-year PFS.

molecular analyses confirmed numerous chromosomal aberrations, some which were found to be independent markers of worse prognosis (2q, 8q gain, 5q, 9p/q, 13q, 15q loss). Additionally, a striking observation was that MAPK pathway mutations were seen in approximately half of males but only in 14% of females. Also, PI3K/mTOR pathway mutations were enriched in GCTs located in the basal ganglia. Together, these observations serve to demonstrate a much more complex underlying biology for these tumors. In contrast, in Western countries the genomic landscape of CNS GCT remains to be elucidated due to reliance on diagnostic tumor markers. The report by Takami and colleagues highlights the conundrum between upfront biopsy/resection for the majority of patients in the Far East compared with selected marker-negative patients in the West. While tissue sampling can provide advances through biologic discovery, this needs to be balanced with any concerns about the risk of added morbidity, metastatic disease along surgical tracts, and the accuracy of tissue representation from biopsies.

Ultimately, the application of molecular technology could drive improved outcomes for GCT patients through the development of tailored, patient-specific treatments. Without this, we are unlikely to make major advancements in treatment and will continue to conduct trials addressing only modifications in radiotherapy dose and/or volumes combined with conventional chemotherapy. The report by Takami and colleagues serves as a prompt for the East and West to consider novel strategies such as liquid biopsy and inclusion of microRNA analyses in lieu of tumor tissue on clinical trials to better inform patient stratification and unravel the biology of these heterogeneous tumors.

Funding

N.G.G. is supported by a Cancer Council of Western Australia Fellowship and the Stan Perron Chair of Paediatric Haematology and Oncology.

References

1. Takami H, Fukuoka K, Fukushima S, et al. Integrated clinical, histopathological, and molecular data analysis of 190 central nervous system germ cell tumors from the iGCT Consortium. *Neuro Oncol.* 2019;21(12):1552–1564.
2. Murray MJ, Bartels U, Nishikawa R, Fangusaro J, Matsutani M, Nicholson JC. Consensus on the management of intracranial germ-cell tumours. *Lancet Oncol.* 2015;16(9):e470–e477.
3. Fujimaki T. Central nervous system germ cell tumors: classification, clinical features, and treatment with a historical overview. *J Child Neurol.* 2009;24(11):1439–1445.
4. Calaminus G, Frappaz D, Kortmann RD, et al. Outcome of patients with intracranial non-germinomatous germ cell tumors-lessons from the SIOP-CNS-GCT-96 trial. *Neuro Oncol.* 2017;19(12):1661–1672.
5. Fangusaro J, Wu S, MacDonald S, et al. Phase II trial of response-based radiation therapy for patients with localized CNS nongerminomatous germ cell tumors: a Children's Oncology Group study. *J Clin Oncol.* 2019:JCO1900701. doi: 10.1200/JCO.19.00701. [Epub ahead of print]
6. Ichimura K, Fukushima S, Totoki Y, et al; Intracranial Germ Cell Tumor Genome Analysis Consortium. Recurrent neomorphic mutations of MTOR in central nervous system and testicular germ cell tumors may be targeted for therapy. *Acta Neuropathol.* 2016;131(6):889–901.
7. Einhorn LH, Foster RS. Bleomycin, etoposide, and cisplatin for three cycles compared with etoposide and cisplatin for four cycles in good-risk germ cell tumors: is there a preferred regimen? *J Clin Oncol.* 2006;24(16):2597–2598; author reply 2598.
8. Osorio DS, Finlay JL, Dhall G, Goldman S, Eisenstat D, Brown RJ. Feasibility of dasatinib in children and adolescents with new or recurrent central nervous system germinoma. *Pediatr Blood Cancer.* 2013;60(9):E100–E102.
9. Calaminus G, Kortmann R, Worch J, et al. SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease. *Neuro Oncol.* 2013;15(6):788–796.
10. Alapetite C, Brisse H, Patte C, et al. Pattern of relapse and outcome of non-metastatic germinoma patients treated with chemotherapy and limited field radiation: the SFOP experience. *Neuro Oncol.* 2010;12(12):1318–1325.
11. Matsutani M. Treatment of intracranial germ cell tumors: the second phase II study of Japanese GCT study group. *Neuro Oncol.* 2008;10(3):420–421. [Conference Abstract]
12. Khatua S, Dhall G, O'Neil S, et al. Treatment of primary CNS germinomatous germ cell tumors with chemotherapy prior to reduced dose whole ventricular and local boost irradiation. *Pediatr Blood Cancer.* 2010;55(1):42–46.
13. Cheng S, Kilday JP, Laperriere N, et al. Outcomes of children with central nervous system germinoma treated with multi-agent chemotherapy followed by reduced radiation. *J Neurooncol.* 2016;127(1):173–180.
14. Goldman S, Bouffet E, Fisher PG, et al. Phase II trial assessing the ability of neoadjuvant chemotherapy with or without second-look surgery to eliminate measurable disease for nongerminomatous germ cell tumors: a Children's Oncology Group Study. *J Clin Oncol.* 2015;33(22):2464–2471.