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Brief Communication

Still divergent but on the way to convergence: clinical practice of CNS germ cell tumors in Europe and North America from the perspectives of the East

Hirokazu Takami, Hideo Nakamura, Koichi Ichimura, and Ryo Nishikawa

Department of Neurosurgery, The University of Tokyo Hospital, Tokyo, Japan (H.T.); Department of Neurosurgery, Kurume University School of Medicine, Kurume, Japan (H.N.); Department of Brain Disease Translational Research, Juntendo University Faculty of Medicine, Tokyo, Japan (K.I.); Department of Neuro-Oncology/Neurosurgery, Saitama Medical University International Medical Center, Hidaka, Japan (R.N.)

Corresponding Author: Hirokazu Takami, MD, PhD, Department of Neurosurgery, The University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan (takami-tky@umin.ac.jp).

Frappaz et al. reported their perspectives on the diagnosis and management of CNS germ cell tumors (GCTs) in Europe and North America (E/NA).[1] Considering the lower frequency in E/NA than in East Asia, it is commendable that they have independently endeavored to establish the standard of care in the frameworks of the International Society of Pediatric Oncology (SIOP) and the Children's Oncology Group (COG). Their paper presents a significant milestone showing their commitments. In parallel, Japan has been playing a leading role in managing CNS GCTs. The Japan Society of Neuro-Oncology guideline appears in the same issue.[2] *Neuro-Oncology* should be congratulated on providing an excellent opportunity to review the longstanding paradigm toward convergence.

The endeavor goes back to 2003 when representatives from 3 continents gathered at the 1st International Symposium on CNS GCTs in Kyoto, Japan, leading to the publication of the consensus statement in 2015 clarifying common clinical practices and differing opinions regarding the significance of cerebrospinal fluid cytology, appropriate tumor marker (TM) cutoffs, and biopsy for bifocal lesions when TMs are elevated.[3] Here, we look back at a few key divergences between E/NA and Japan.

Considerable differences in treatment have existed across countries. Carboplatin + etoposide and whole ventricular irradiation (WVI) for germinomas have been consistently used in 2 Japanese clinical trials since 1995, underpinned by common relapses in-and-around the ventricles. Results from SIOP-CNS-GCT-96[4] and COG-ACNS0232 demonstrated that strategies employing radiation therapy to the primary tumor alone in germinoma resulted in unacceptable rates of distant failures, most commonly along the subependymal surfaces of the ventricles. The treatment was shifted to WVI and platinum-based chemotherapy. For nongerminomatous GCTs (NGGCTs), strategies remain divergent; local irradiation has been the standard of care for localized disease in SIOP,[5] while craniospinal irradiation (CSI) plus local irradiation in ACNS0122,[6] WVI and local irradiation in ACNS1123,[7] and WVI plus spinal canal irradiation depending on the response to chemotherapy in ACNS 2021 (now recruiting) are employed in COG. In Japan, CSI has been preferred for a poor-prognosis subgroup with malignant histology including choriocarcinoma, yolk sac tumor, and embryonal carcinoma. The identification of a poor-prognosis subgroup, which indicates cases with the abovementioned malignant components dominant in tissues or cases with human chorionic gonadotropin >2000 IU/L or alpha-fetoprotein (AFP) >2000 ng/mL, is a contribution from Japan; 5-year survival is <50%, which is significantly worse than that of other NGGCTs, thus requiring intensive chemotherapy and CSI. SIOP now recognizes "high-risk" NGGCTs for AFP >1000 ng/mL or age <6 years; treatment is upfront high-dose chemotherapy and local irradiation if the tumor is localized.

A major difference also lies in diagnostics. In Japan, histopathological diagnosis has been the gold standard whereas in E/NA, histopathological investigations are not required when TMs are elevated (Figure 1). Therefore, we specifically addressed the advantages and disadvantages of histopathological diagnosis.[2] Notably, direct comparison of treatment outcomes among Japan/E/NA proves difficult. While highly secreting tumors such as yolk sac tumor and choriocarcinoma are rightly diagnosed as NGGCTs in any criteria across countries, germinoma and teratoma with elevated TMs can be heterogeneously diagnosed and treated among different protocols.

The results of a clinical trial in Japan (1995–2003) will soon be available, as the extended observational study is now closing. The second clinical trial (2010–) is also finalizing

<table>
<tr><th>COG</th><th>SIOP</th><th>Japan</th></tr>
<tr><td><u>Germinoma</u>

HCG ≦ 100 IU/l and
AFP ≦ 10 ng/ml and
Histopathological Dx
OR
Bifocal tumor with negative tumor marker w/o DI</td><td><u>Germinoma</u>

HCG ≦ 50 IU/l and
AFP ≦ 25 ng/ml and
Histopathological Dx
OR
Bifocal tumor with negative tumor marker</td><td rowspan="2"><u>Germinoma</u>
(Histopathological Dx)</td></tr>
<tr><td><u>NGGCT</u>

HCG > 100 IU/l or
AFP > 10 ng/ml or
Histopathological Dx</td><td><u>NGGCT</u>

HCG > 50 IU/l or AFP > 25 ng/ml or Histopathological Dx</td></tr>
<tr><td colspan="2"></td><td><u>Intermediate prognostic group</u>
• ImT
• Teratoma with somatic-type malignancy
• Mixed GCTs mainly composed of germinoma and teratoma</td></tr>
<tr><td colspan="2"></td><td><u>Poor prognostic group</u>
• CC, EC, YST
• Mixed GCTs mainly composed of these components
• HCG > 2000 IU/L or AFP > 2000 ng/ml</td></tr>
</table>

Figure 1. Comparison of diagnostic criteria for germinoma and nongerminomatous germ cell tumors among different clinical trials worldwide. AFP, alpha-fetoprotein; CC, choriocarcinoma; COG, Children's Oncology Group; DI, diabetes insipidus; Dx, diagnosis; EC, embryonal carcinoma; GCT, germ cell tumor; HCG, human chorionic gonadotropin; ImT, immature teratoma; NGGCT, nongerminomatous germ cell tumor; SIOP, International Society of Pediatric Oncology; w/o, without; YST, yolk sac tumor.

its accrual. A new clinical trial by the Japan Children's Cancer Group will commence soon. Germinomas will be treated with cisplatin + etoposide alternating with carboplatin + etoposide and randomized to 18 or 23.4 Gy WVI, and malignant NGGCTs treated with cyclophosphamide + cisplatin + etoposide with randomization to either intrathecal methotrexate with local irradiation or CSI.

Despite the remaining gaps between Europe, North America, and Japan, convergence in management is progressing, such as in identifying the appropriate radiation field for germinoma. Enthusiasm toward reducing the treatment burden on pediatric/adolescent patients is shared across continents. Optimization of diagnosis and treatment by further clinical studies is warranted to achieve the worldwide standards. Biological studies based on surgically obtained tissues should be pursued. The Malignant Germ Cell International Consortium from E/NA is also expected to contribute to treatment development. This issue of *Neuro-Oncology* provides strong momentum for the management paradigm of this rare disease to move forward worldwide. Now is the time to plan the 6th intracranial GCT symposium for further discussion.

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