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Original Research

Primary central nervous system germ cell tumors in children and young adults: A review of controversies in diagnostic and treatment approach

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ABSTRACT

Primary central nervous system (CNS) germ cell tumors (GCT) are a rare heterogenous group of cancers, arising most commonly in the second decade of life. Through several clinical trials conducted around the world by various groups, the treatment approach for CNS GCT has advanced substantially with generally improved overall outcomes. In recent years, the goal of clinical trials has been focused on reduction of the radiotherapy burden and minimization of long-term toxicity. This review summarizes the current diagnostic and treatment regimens for CNS GCT, examines the controversies associated with these approaches, gaps in contemporary knowledge, and underscores the challenges we face. We also explore future directions in the management of CNS GCT with the ultimate overall aim of preserving curative outcomes, identifying novel biomarkers, and mitigating neurocognitive, endocrine, and psychological toxicity through prospective clinical studies.

Introduction

Central nervous system (CNS) germ cell tumors (GCT) are rare malignant tumors seen in adolescents and young adults (AYA) with a median age of 16 years [1]. In Western countries, CNS GCT accounts for approximately 3-5% of all primary CNS tumors in children [2,3]. The incidence is substantially higher in Asian countries such as Japan and Taiwan, where they account for 10-15% of all pediatric CNS tumors. The exact genetic and/or environmental reasons for this variance are yet to be identified [3,4]. CNS GCT are more common in males, especially among pineal primary GCR. On the other hand, suprasellar GCT show a slight female preponderance [1,5].

CNS GCT are classified into germinoma and non-germinomatous GCT (NGGCT), where germinoma account for 2/3 of all CNS GCT [2,3]. NGGCT include yolk sac (endodermal sinus) tumor, choriocarcinoma, embryonal carcinoma, teratoma, or mixed GCT. CNS GCT predominantly present in midline structures, favoring the pineal or suprasellar region [6]. A smaller proportion present as concurrent suprasellar and pineal bifocal lesions, while 5-10% are non-midline basal ganglia and thalamic lesions.

Pathogenesis and genomic landscape of CNS GCT

While the pathogenesis of CNS GCT is unknown, the embryonic cell theory proposes that they arise from pluripotent embryonic cells that evaded normal neural tube development. The more recent germ cell theory supports aberrant primordial germ cell (PGC) migration to the developing fetal genital ridge [7,8]. Pure germinomas and migrating PGCs share the unique characteristic feature of global DNA hypomethylation, possibly indicating the cell of origin for these tumors [9,10]. Germinoma cells molecularly resemble pluripotent human embryonic stem cells with upregulation of self-renewal genes such as *OCT4, NANOG, and KLF4. BAK1* deletions may also play a role in GCT formation by impairing apoptosis of mis-migrated PGCs due to down regulation of the KIT/KITLG signalling pathway [11].

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Takami *et al* reported that germinoma had a transcriptomic profile representative of PGCs with high meiosis/mitosis potentials *(PIWIL1, DAZL, DDX4, NANOS3,* and *ERVW-1* and cancer-testis antigen (*CTA)* genes such as *MAGEB1, MAGEB16*, and *MAGEC2)* [12]. NGGCT are characterized by neuronal differentiation, epithelial-mesenchymal transition, or over-expression of Wnt/β-catenin pathway associated genes [13,14]. Emerging techniques such as single-cell-RNA-sequencing could further help dissect their intratumoral heterogeneity [15].

Recently, chromosome 12p gain has been shown to predict outcomes in GCTs, with shorter progression-free survival (PFS) and overall survival (OS). They are present in 30% of CNS GCTs, more frequently in NGGCT (~50%). Additionally, 12p copy number status was shown to be shared among different histological components in mixed GCTs, suggesting 12p gain as an early event in tumorigenesis [16].

Although chromosomal instability is characteristic of all CNS GCT, somatic KIT/RAS and PI3K/ AKT1 mutations have been described more frequently in germinoma [17], while MAPK pathway alterations favor thalamic CNS GCT [18]. Germinomas express genes linked to immune response such as CCL18, CD72, and IL6R, consistent with cytotoxic T-lymphocyte infiltration [19]. Germinomas can overexpress PD-L1, whereas tumor-infiltrating leukocytes express PD-1. These could potentiate tumor growth by suppressing antitumoral immune response and in turn, provide novel therapeutic targets [20,21]. Segregation into GCT histological subtypes through unsupervised hierarchical transcriptomic clustering has been recently demonstrated. Although some germinomas showed immune-cell infiltration, NGGCT had significantly higher immune-cell infiltration, indicating an immune-suppression phenotype [12]. Furthermore, integrated transcriptome/methylation analysis clustered germinoma/seminoma and non-germinoma/non-seminoma separately, with two distinct germinoma subgroups based on tumor content and MAPK pathway alterations. Group 1 had noticeably lower tumor content and enriched for immune-related genes compared to Group 2. Although the difference in PFS (75% *versus* 100%) was not statistically significant, it was concordant with previous reports of the prognostic value of tumor content in germinoma and may influence risk stratification and treatment in the future [12,22,23]. Germinomas overexpressing CTAs were associated with high tumor content, which could be considered as a novel germinoma characteristic ($p < .0001$) [12].

Constitutive sex chromosomal abnormalities such as Klinefelter's syndrome (47, XXY) and Down syndrome are associated with a higher risk of CNS GCT while germline associations with JMJD1C, encoding histone deacetylase and a co-activator of the androgen receptor, have been reported in Japanese children with CNS GCT [17].

Diagnosis

Clinical presentation

Pineal tumors are associated with increased intracranial pressure due to obstructive hydrocephalus, presenting with early morning headaches, blurred vision, somnolence, ataxia and emesis in older children and growing head circumference in infants. Parinaud's syndrome (upward gaze palsy, nystagmus and pupillary hyporeflexia) is common in pineal tumors [24]. Suprasellar tumors present with hypothalamic-pituitary axis dysfunction, and endocrinopathies such as diabetes insipidus, precocious puberty, growth failure and hypopituitarism [24]. Basal ganglia GCT are associated with hemiparesis/motor weakness, cranial neuropathy, and neurocognitive dysfunction, with a symptom interval lasting months-to-years [25]. Pineal or basal ganglia germinoma can present with occult suprasellar disease resulting in endocrinopathies, primarily diabetes insipidus [26,27].

Diagnostic imaging

MRI of the brain and spine with and without contrast is the study of choice. CT scan, however, is superior in identifying calcification and intracranial hemorrhage [28]. In general, germinomas have a homogenous appearance and enhance diffusely with contrast, while NGGCT are more heterogenous and can present with hemorrhage, especially common with choriocarcinoma [28,29]. Despite imaging characteristics, distinguishing germinoma from NGGCT remains a challenge if based solely on MRI features.

Controversies in neuroradiological tumor evaluation

The heterogeneity in neuroradiological criteria to measure CNS GCT and response to therapy between multiple cooperative groups such as Children's Oncology Group (COG) and International Society of Paediatric Oncology (SIOP), has led to significant challenges in consensus agreement on the most appropriate assessment methods [30]. Variation in appraising solid and cystic components in bidirectional or volumetric dimensions in diverse intracranial sites (pineal, hypophyseal, basal ganglia, thalamic and spinal) or the pituitary bright spot for indications of diabetes insipidus, with conventional or novel sequencing approaches, creates inconsistency in defining complete response (CR), stability, or progression.

While reasonably straightforward to assess solitary lesions, bifocal or multifocal disease pose a significant challenge. Should an 'overall assessment' (e.g., partial response defined by 50% reduction in the sum of 2D and 3D measurements of up to 4 target lesions) be sufficient? Or should an additional response assessment for individual target lesions be considered to optimise radiotherapy fields or dosimetry?

Future trials should incorporate such questions to be prospectively evaluated. A consensus statement by COG and SIOP proposes several recommendations that may help homogenise practice, facilitate direct comparability of data and inform future standards of care [31].

Utility of tumor markers in the diagnosis of CNS GCT

GCT can secrete protein markers into the blood and cerebrospinal fluid (CSF), which can be measured and utilized for diagnostic and therapeutic monitoring. The commonest tumor markers used clinically are alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (HCGβ).

A CNS mass with serum AFP elevation above institutional standards (or >10ng/mL in serum or >2ng/mL in CSF) is considered diagnostic for a CNS NGGCT, without requiring a biopsy, with a caveat of physiological AFP elevation from embryonic development in young children less than 2 years of age.

HCGβ elevation in the presence of a CNS mass is considered diagnostic for a GCT, but could represent either histology, since germinoma, choriocarcinoma, embryonal carcinoma and immature teratoma can all secrete HCGβ at varying levels [32,33].

PLAP (fetal isoenzyme of alkaline phosphatase), shown to be relatively sensitive and specific for germinoma and thought to be beneficial when AFP and HCGβ are negative in serum and CSF [34]. Unfortunately, PLAP testing is not readily available in many institutions and its use remains mostly experimental.

An emerging biomarker tool is microRNAs (miRNAs). Serum and CSF miR-371a-373p and miR-302/367 clusters detected in patients with NGGCT have demonstrated higher sensitivity and specificity than standard tumor markers in testicular GCT, with potential diagnostic and prognostic benefit [35,36]. 27 novel miRNA candidates with differential expression amongst subtypes were identified but overexpression of miR-214-3p in NGGCT cells were associated with cisplatin resistance through repression of BCL2-like pro-apoptotic proteins.[37] A recent study evaluated the diagnostic suitability of miR-371a, miR-372, miR-367 and miR-302d in serum and CSF, particularly in tumor marker-negative germinoma, providing further evidence of the feasibility, validity and accessibility of serum as a less invasive biomarker than CSF. This could allow differentiating CNS GCT from other tumors with similar

radiological findings, monitoring therapy response and identifying early relapse during follow-up [38].

Lastly, *KIT* and *NRAS* ctDNA (circulating tumor DNA) and CSF metabolites can serve as promising novel biomarkers for CNS-GCTs and could differentiate germinomas from NGGCTs [39], but require prospective validation prior to clinical adoption.

Controversies in the utility of tumor markers in CNS GCT

A midline CNS tumor with low-level HCGβ elevation can be sufficient evidence for germinoma diagnosis, although the exact threshold of HCGβ elevation is debatable. Stringent European diagnostic criteria for germinoma allow only HCGβ elevation up to 50 mIU/mL while >50 mIU/mL is treated as an NGGCT [40]. In contrast, the COG allows HCGβ levels up to 100 mIU/mL to be treated as germinoma, including bi-focal disease [41]. Interestingly, all five germinoma patients with HCGβ up to 200 mIU/mL treated on the latest Brazilian clinical trial are currently alive, without tumor recurrence (personal communication with Dr. Andrea Cappellano). Conducting clinical trials across different cooperative groups using similar tumor marker cut-offs may help address this dilemma.

Whilst these thresholds are considered standard practice in respective countries, with minimal adverse impact on outcomes, diagnosing a CNS germinoma without surgical biopsy remains controversial. In Japan, upfront surgical biopsy/resection is recommended for all patients with CNS GCT for pathological confirmation, since entities such as Langerhans cell histiocytosis have been reported to secrete low levels of HCGβ [42]. The Japanese also uniquely classify CNS GCT into good, intermediate, and poor prognostic groups based on diagnostic histopathology and tumor markers [43].

Histopathology in CNS GCT

Sole reliance on traditional non-invasive diagnostic modalities such as clinical features, radiology, and tumor markers, although indispensable to management, has limitations. Histopathology provides an additional layer of diagnostic certainty, as there are reports of marker-positive germinoma, such as HCGβ-secreting syncytiotrophoblastic giant cells (STGC), marker-negative-NGGCT, and misdiagnosis as GCT in the literature [44].

CNS germinoma is morphologically similar to dysgerminoma (in the ovaries) and seminoma (in the testis), characterized by large monomorphic cells with clear cytoplasm, separated by thin fibrous septa into lobules, with prominent lymphocytic infiltrate and typical positive immunohistochemical (IHC) staining for PLAP, OCT4, SALL4 and c-kit. NGGCTs constitute several subtypes with varied histological features. Teratoma demonstrate some/all three embryonal layers (mesoderm, endoderm, ectoderm). Yolk sac (endodermal sinus) tumor are typically large, polygonal cells with well-defined borders with positive AFP on IHC. Embryonal carcinomas are large, highly irregular, pleomorphic cells with high mitotic/proliferative rate and necrosis, with unique membranous staining for CD30. Lastly, choriocarcinoma are highly malignant tumors that display extensive hemorrhage with necrosis with HCGβ positivity on IHC.

Controversies in histopathologic diagnosis in CNS GCT

Even with the combined information from imaging, tumor markers and histopathology/IHC, diagnostic dilemma can still occur. Histopathology without an adequate and representative biopsy specimen can increase the risk of misrepresenting the entire tumor and misdiagnosis [45,46]. While emerging technology such as DNA methylation profiling and genome sequencing can help facilitate an integrated diagnosis, these technologies are similarly limited by sampling error. Novel approaches such as CSF miRNA, could potentially help address these issues and refine our diagnostic approach.

Disease staging of CNS GCT

Approximately 15% of CNS GCT can have leptomeningeal disease at diagnosis [24]. Therefore, MRI of the brain and spine is critical for appropriate staging. Additionally, CSF should be collected for cytological analysis whenever a lumbar puncture can be safely performed. Lumbar puncture is considered standard-of-care for staging (as opposed to intraventricular CSF sampling) [47]. Patients with positive CSF cytology are typically considered to have metastatic disease, even with a normal MRI of the spine [47]. While there is no established staging system for CNS GCT, most physicians utilize the TM/Chang system employed for other CNS tumors.

Controversies in staging of CNS GCT

The role of CSF cytology in staging CNS GCT is widely accepted, where positivity is treated as metastatic disease. Positive CSF cytology did not correlate with the presence of spinal disease on MRI, and that avoiding craniospinal irradiation (CSI) in germinoma patients with positive CSF cytology without spinal lesions on imaging still achieved excellent PFS, comparable to those treated with CSI [48]. While intriguing and potentially clinically significant, these results need validation in a larger cohort, as it would represent significant deviation from current North American and European practice.

Treatment

Role of surgery

Tissue diagnosis

In cases of tumor marker elevation within specific parameters and diagnostic for either germinoma or NGGCT, invasive surgery for tissue biopsy could potentially be avoided. Negative or inconclusive/non-diagnostic tumor markers, however, would be a compelling indication for obtaining tissue and establishing a histological diagnosis.

CSF Diversion

Pineal GCT often present with obstructive hydrocephalus, which requires CSF diversion either through an endoscopic third ventriculostomy (preferred) or a ventricular shunt placement (risk for peritoneal seeding). Occasionally, it is possible to avoid these procedures after an initial external ventricular drain (EVD) placement if chemotherapy is initiated promptly, as CNS GCT are commonly chemotherapy-sensitive and may shrink sufficiently for resumption of normal CSF flow in days/weeks. Importantly, when CSF diversion such as ETV is performed, simultaneous tumor biopsy has been shown to be safe and is generally recommended when clinically feasible [49].

Second-look surgery

For patients with incomplete response to chemotherapy, there is a definitive role for second-look surgery. This is either to achieve CR prior to radiation therapy (RT), evaluate for growing teratoma syndrome (GTS)/fibrosis/scar, or to intensify therapy before moving to RT in cases with viable tumor.

Controversies in surgical management of CNS GCT

While surgery of the residual primary mass after induction chemotherapy in NGGCT is highly recommended, the role of second-look surgery in germinoma is less clear. Out of 11 patients who underwent second-look surgery after finishing chemotherapy on COG ACNS1123 stratum 2, none had viable germinoma elements [41]. Furthermore, outcomes for germinoma patients with residual disease after radio-chemotherapy on SIOP CNS GCT 96 were not statistically different to those without residual disease, which questions the utility of a higher dose RT for residual germinoma [40]. Second-look surgery should be

strongly considered in germinoma and NGGCT, if discordance occurs between tumor marker and radiographic response, which could suggest GTS.

While there is a growing preference for endoscopic techniques, there are case reports suggesting an association between surgical tracts (biopsy/endoscopy tract, EVD) and site of disease relapse [50–52]. Moreover, in the COG Phase II trial of response-based RT for patients with localized germinoma, 3 of 8 relapses (37.5%) occurred along a surgical tract [53]. These findings raise the question of including surgical tracts in the RT field. A secondary analysis of the COG ACNS1123 data is underway and may help answer this question.

Role of chemotherapy and radiation therapy

Standard-of-care strategies comprise of surgery, chemotherapy, and RT with a focus on treatment reduction and minimising toxicity sequelae. There is, however, considerable variation in North American, European, and Asian approaches.

Germinoma

Historically, CSI alone has achieved high cure rates for both localized and metastatic disease [54]. Chemotherapy-only approaches have also been tried. While effective, they did not produce durable remission and historically led to a less than 50% cure rate [55,56]. In recent years, neoadjuvant chemotherapy has been successfully incorporated in the treatment regimens for germinoma, with the intention of reducing the dose and field of RT, especially for those with localized disease [40,57].

Clinical trials by large cooperative groups such as COG and SIOP have endeavoured to refine chemo-irradiation strategies for localised disease. Early single institution studies demonstrated excellent radiological responses to cyclophosphamide or carboplatin monotherapy and dropping tumor bed boost from 50 Gy to 30 Gy, with preserved OS [58,59]. A subsequent COG clinical trial demonstrated a 3-year EFS of 92% ± 8% in 12 evaluable patients receiving alternating induction chemotherapy cycles of cisplatin-etoposide and cyclophosphamide-vincristine followed by 30.4Gy focal RT [60].

Chemoradiotherapy – role of focal RT

The SFOP TGM-TC-90 study demonstrated germinoma recurrence in 10 of 60 cases, 8 in periventricular location, after local RT of 40Gy with a 2-cm margin [61]. The SIOP CNS GCT 96 trial treated 65 patients with localized disease with two alternating courses of carboplatin-etoposide with ifosfamide-etoposide (CarboPEI), followed by 40 Gy focal radiotherapy, demonstrating no 5-year OS or EFS differences, but a PFS of 88% ± 4%. Six of the 7 relapses were ventricular, outside the primary RT field. Forty-five metastatic patients had an EFS and OS of 98% ± 2.3%, in response to 24 Gy CSI with 16Gy focal boosts to primary tumor and metastatic sites [40]. The SIOP CNS GCT II trial thus adopted 24 Gy whole ventricular irradiation (WVI) instead of focal irradiation for patients in CR after CarboPEI. Interim results report an EFS of 98% at 4 years for these 58 patients, prompting consideration as standard consolidation treatment for localised germinoma [62].

Chemoradiotherapy – role of WVI

Two early Japanese studies indicated equivalent efficacy and tolerability of post-RT chemotherapy regimen (cisplatin-vinblastine-bleomycin and cisplatin-etoposide), with whole brain irradiation (WBI) of 50Gy resulting in recurrences and significant hypothalamic dysfunction [63]. A University of Tokyo study demonstrated efficacy of pre-RT cisplatin-carboplatin combination in neuro-hypophyseal germinomas and intermediate-risk patients but not in the poor-prognosis group, with WBI of 30Gy, 30-62Gy and 50-55Gy doses respectively. Matsutani *et al.* then utilized extended local RT of 24Gy following CARE (carboplatin/etoposide) chemotherapy without the need for WBI, resulting in 10-year OS of 98%, reducing neurocognitive damage and improving quality of life [64]. The current Japanese study (iRCTs031180223) has completed enrolment, utilising 23.4Gy and CARE chemotherapy approach [65]. Chemotherapy followed by 21.6-25.5 Gy WVI and local 30-30.6 Gy boost appeared to be effective in localized pure CNS germinoma with neurocognitive preservation in a multi-institutional American study [66]. The COG conducted a response-based dose-reduction trial (ACNS1123; Stratum 2) for patients with localized germinoma with 18Gy WVI and 12Gy tumor bed boost for patients in a CR after 4 courses of carboplatin-etoposide [53]. Seventy-four patients achieved a 3-year PFS of 94.4% ± 2.7%. Interestingly, a Canadian retrospective study demonstrated an EFS of 96% and OS of 100% with carboplatin and etoposide induction followed by 24Gy WVI without a boost [67].

Chemoradiotherapy for Bi-focal, non-midline, and metastatic germinoma

Bifocal germinomas, by consensus, are treated as locoregional (pineal and suprasellar) rather than metastatic tumors, only if it meets specific tumor marker criteria (which varies by study) and has classic radiological appearance [68]. In smaller studies, when treated with combined chemoradiotherapy approach similar to those for localized disease, bifocal germinomas have a 3-year PFS and OS of 100% [69]. However, data from Japan has shown that not all bifocal lesions are germinomas ~ 3.4% have NGGCT elements, which raises the question whether biopsies should be considered for bifocal germinomas [70]. Basal ganglia/thalamus germinomas (BGTGs) are more challenging to treat, due to their rarity and poorly defined imaging characteristics. CSI, WBI, WVI, and focal RT have all been utilized with unclear consensus on standard of care [71]. However, recent studies suggest modest outcome for these patients, even when treated without spine or whole brain RT, supporting the role for reduced dosed and field RT [25,72]. These findings remain to be validated, and the inclusion of these patients in prospective clinical trials should be an essential undertaking. Successful treatment of metastatic germinoma requires CSI. While European standard of care is 24Gy CSI with 16Gy boost to primary and metastatic sites without chemotherapy, another group reported successful treatment with pre-RT chemotherapy without a boost dose [73]. Furthermore, the latest trial in Korea (SMC-G13) has demonstrated the success of utilizing neoadjuvant chemotherapy followed by 18 Gy CSI and 12 Gy boost [74].

Controversies in medical management of germinoma

The above discussion highlights the heterogeneity of management approaches across continental groups and raises several questions about the optimal treatment strategy; duration of chemotherapy (4 *versus* 6 induction cycles), field of RT (focal *versus* WVI), RT doses (18 *versus* 24Gy), RT boost (yes or no).

Non-germinomatous germ cell tumors

Compared to germinoma, NGGCT are associated with poorer prognosis and higher rates of recurrence. Previously attempted single modality treatment with either full-dose CSI or chemotherapy-only approaches were less effective and associated with unacceptably high rates of disease recurrence [55,75-77]. Although it is clear that a multi-modality approach with induction chemotherapy followed by RT is key to outcomes [47], chemotherapy choices and RT field/dose remain undefined. As CSI and WBI are associated with significant long-term toxicity, the current landscape of clinical trials has been focused on de-escalation of RT exposure with risk stratification based on disease stage and response to induction chemotherapy. For patients with metastatic disease, chemotherapy followed by CSI is widely considered as the optimal therapy. Nevertheless, for patients with localized disease, the ideal treatment approach remains unclear.

Chemoradiotherapy for localized disease

Several publications suggested that the use of chemotherapy and focal RT for patients with localized NGGCT was effective, resulting in PFS of 80-85% [78]. Similarly, in the SIOP CNS GCT-96 trial, localized disease was treated with four cycles of induction chemotherapy followed by focal (IF) RT to 54 Gy, leading to a 5-year PFS and OS of 72% ± 4% and 82% ± 4%, respectively [79]. For "intermediate risk" patients, the Japanese group reported an excellent 5-year OS rate of 89% with chemotherapy followed by WVI. In contrast, the COG ACNS0122 study treated all patients (including patients with localized disease) with six cycles of induction chemotherapy followed 36 Gy CSI + IF boost to 54 Gy, with excellent outcomes [80]. Considering these data, COG ACNS1123 stratum 1 was developed, utilizing the same induction chemotherapy backbone as ACNS0122, but with a response-based RT plan. This study treated good responders to induction chemotherapy with WVI of 30.6 Gy, followed by focal 23.4 Gy boost. Despite excellent outcomes, this study was closed prematurely as it met early stopping rules, which is further discussed in the controversy section below.

Chemoradiotherapy for metastatic disease

For patients with metastatic disease, chemotherapy followed by CSI is considered standard-of-care. In the ACNS0122 study, 25 patients with metastatic disease had a 5-year EFS and OS of 84% ± 4% and 93% ± 3%, respectively [80]. In the SIOP CNS GCT-96, patients with metastatic NGGCT received four courses of chemotherapy consisting of cisplatin, ifosfamide, and etoposide followed by 30 Gy CSI and boost for the primary disease site. The five-year PFS and OS were 68% ± 9% and 75% ± 8%, respectively [79]. Based on these results, while there is no universally accepted treatment approach, induction chemotherapy followed by 36 Gy CSI with a boost to 54 Gy is generally considered standard-of-care.

Controversies in field and dose of RT for CNS NGGCT

There is significant heterogeneity in management approaches across continental groups, which raises several questions regarding optimal chemoradiation strategies; chemotherapy drugs/doses and RT field/dose. In addition, the standard-of-care treatment approach for localized NGGCT remains unclear. As stated above, ACNS1123 unfortunately closed prematurely as it met early stopping rules, although in retrospect, two patients were later found to have been ineligible to receive reduced-dose RT. Nevertheless, the 3-year PFS and OS for patients who were eligible for this dose-reduced RT plan were 87.8% and 92.4%, respectively [81]. While these outcomes are excellent with PFS similar to those treated with CSI on ACNS0122, it was noted that there was an increased number of spinal relapses among the small number of patients who had disease recurrence. This ultimately prompted the initiation of ACNS2021, which aims to determine if the re-inclusion of spinal canal RT will decrease the number of spinal/metastatic recurrences while maintaining the outcomes previously reported on the ACNS0122 trial.

Future plans

Advancements in cancer genomics have led to improved understanding of the molecular underpinnings of cancers, including those of CNS GCTs. Activating mutations in the MAPK pathway (including KIT and RAS) and the PI3K/mTOR pathway are common genetic aberrations in CNS GCTs [17,18]. Interestingly, KIT overexpression is seen in the majority of pure germinomas, and virtually absent from NGGCTs without a germinomatous component. With the recent development of molecularly selective inhibitors for many targets including KIT and RAS, CNS germinoma is a particularly intriguing disease for targeted therapy approaches. However, the role of targeted inhibition in CNS NGGCTs remains unclear given their intra-tumor heterogeneity, and lack of clear molecular targets [82].

Novel therapeutic approaches can potentially augment the current therapeutic paradigm for CNS GCT. In addition to targeted therapy, immune checkpoint inhibitors may play a role, especially in NGGCT [21]. These approaches could eventually decrease or eliminate the need for cytotoxic chemotherapy, and in turn reduce the risk of oto-/nephrotoxicity, serious allergic reactions, secondary malignancy, and infertility. Avoiding chemotherapy-driven hospital admissions may also have a significant positive impact on the AYA population's quality of life. While promising, the development of clinical trials utilizing these novel therapies (such as RAS, mTOR, and KIT inhibitors) must overcome numerous challenges prior to their initiation.

A key challenge faced by researchers studying primary CNS GCTs is the lack of an established *in-vitro* & *in-vivo* model. Numerous attempts at establishing GCT cell lines that stably express mutant-KIT have been attempted without success. While Tcam2 (seminoma cell line with BRAFV600E mutation) and YST1 cells (malignant schwannoma cell line) have been used as surrogates, neither are ideal models for primary CNS GCT [82]. Although the current standard-of-care for germinoma leads to excellent outcomes (albeit with significant toxicities), efforts should be focused on safely incorporating novel therapy approaches into clinical trials by utilizing the robust data for targeted agents (e.g. KIT inhibitors) that had been shown to cross the blood-brain-barrier in other tumors.

To this end, the Pacific Pediatric Neuro-Oncology Consortium (PNOC) GCT working group, comprised of neuro-oncologists from North America, Australia, Europe, Africa, the Middle East, and Asia, led by Drs. Mohamed Abdelbaki and Girish Dhall, is focused on the design and conduct of prospective studies to investigate the biology of CNS GCTs, the role of CSF miRNA as biomarkers, and to elucidate the prognostic role of genetic aberrations. Clinical trial concepts are also being explored, to investigate the roles of immunotherapeutic approaches. In addition, since RT is the mainstay of CNS GCT therapy, consideration for prospective neuroprotective measures to preserve long-term cognitive and endocrine function will be included in upcoming trials. The working group has also initiated retrospective international multi-institutional studies to examine the association of treatment modalities on outcomes in residual disease in germinomas, primary metastatic germinomas and recurrent/relapsed GCTs that may help update future practice. Interim analyses of these have been presented at ISPNO 2022.

This review from the group highlights current gaps in diagnostic, therapeutic and biomarker monitoring approaches for GCTs that could be filled by safely incorporating novel molecular methodologies such as genomic, miRNA, epigenetic, tumor microenvironment and pharmacogenomics profiling into future prospective clinical trials, to inform standards of care that offer optimal molecularly-selective personalized therapy for all stages of disease presentations, resulting in better survival outcomes, reduced burden of treatment toxicity and improving quality of life for our patients, with a cross-continental collaborative approach.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Kee Kiat Yeo: Conceptualization, Methodology, Writing – original draft. **Sumanth Nagabushan:** Conceptualization, Methodology, Writing – original draft. **Girish Dhall:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Mohamed S. Abdelbaki:** Conceptualization, Methodology, Supervision, Writing – review & editing.

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