Multi-institutional analysis of central nervous system germ cell tumors in patients with Down syndrome

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April 11, 2022

Abstract

Purpose: Primary germ cell tumors (GCTs) are the most common central nervous system (CNS) neoplasm in patients with Down syndrome (DS). However, a standard-of-care has not been established due to a paucity of data. Methods: A retrospective multi-institutional analysis was conducted, in addition to a comprehensive review of the literature. Results: Ten patients from six institutions (five USA, one Brazil) were identified, in addition to 31 patients in the literature from 1975 to 2021. Of the 41 total patients (mean age 9.9 years; 61% male), 16 (39%) had non-germinomatous germ cell tumors (NGGCTs), 16 (39%) had pure germinomas and eight (19.5%) had teratomas. Basal ganglia was the most common tumor location (n=13; 31.7%), followed by posterior fossa (n=7; 17%). Nine patients (22%) experienced disease relapse or progression, of which four died from tumor progression (one germinoma, three teratomas). Sixteen patients (39%) experienced treatment-related complications, of which eight (50%) died (five germinomas, three NGGCTs). Of the germinoma patients, two died from chemotherapy-related sepsis, one from post-surgery cardiopulmonary failure, one from pneumonia and one from Moyamoya following radiation-therapy (RT). Of the NGGCT patients, one died from chemotherapy-related sepsis, one from post-surgical infection and one from pneumonia following surgery/chemotherapy/RT. Three-year overall survival was 66% for all histological types – 62% germinomas, 79% for NGGCTs, and 53% for teratomas. Conclusion: Patients with DS treated for CNS GCTs are at an increased risk of treatment-related adverse events. A different therapeutic approach may need to be considered to mitigate treatment-related complications and long-term neurocognitive sequelae.

INTRODUCTION

Central nervous system (CNS) germ cell tumors (GCTs) make up <4% of primary pediatric brain tumors, with incidence rates increasing among males, individuals <20 years old and Eastern Asian populations.[1] Central nervous system GCTs can be broadly classified as germinomas, nongerminomatous GCTs (NGGCTs) or teratomas.[1] Based on histological components, NGGCTs can be classified into embryonal carcinomas, yolk sac tumors (YSTs), choriocarcinomas, GCTs with mixed components (mixed GCTs) or germinomas with syncytiotrophoblastic giant cells (STGCs).[1]Teratomas may be divided into mature teratomas, immature teratomas or teratomas with malignant transformation.[1]

Down syndrome (DS) has classically been associated with higher rates of blood cancers such as acute myeloid leukemia (AML).[2]The incidence of solid tumors in patients with DS is rare, yet GCTs have been found to make up a disproportionate number of intracranial tumors as compared to the general population.[3] Though associations between CNS GCTs and DS have been reported, the small number of cases is limiting; the most recent literature review reported just 21 patients with CNS GCTs and DS, with almost all studies arising from Japan or China.[4] This paucity of cases, particularly of those from Northern America, has limited our understanding of this patient population.

The standard of care for CNS GCTs includes a combination of surgery, platinum-based chemotherapy and radiotherapy (RT), with specific treatments varying by tumor subtype and individual institution.[1] In patients with DS, treatment is complicated by their increased risk of developing acute and long-term treatment-related adverse effects. Patients with DS are at an increased risk of RT-related cognitive impairments and cerebrovascular disease given their baseline cognitive impairments, decreased cerebral volume and predisposition to degenerative neurologic disease.[5,6] Moreover, it is well-documented that patients with DS are highly susceptible to toxicities related to standard chemotherapy drugs used in AML; these include treatment-related infection, mucositis from methotrexate therapy, anthracycline-induced cardiomyopathy and even fatal neurotoxicity.[5,7]

Due to the complexity of care and rarity of cases, a standard treatment approach that promotes both optimal survival and minimization of treatment-related adverse effects in patients with CNS GCTs and DS has not been established. Here, we describe a multi-national and multi-institutional retrospective analysis of patients diagnosed with DS and CNS GCTs, in addition to a review of the literature.

METHODS

Study Design and Participants

A comprehensive literature search was performed using PubMed/MEDLINE and Google Scholar. Major academic institutions across the USA, Brazil and Australia were systematically contacted and provided with a de-identified data collection form. Each participating center received approval from their local Institutional Review Board.

Data

The following data were collected: Sex, age at diagnosis, presenting symptoms and duration, ethnicity, primary tumor site, histology, serum/cerebrospinal fluid (CSF) tumor markers including beta human chorionic gonadotropin (bHCG) and alfa fetoprotein (AFP), extent of surgical resection, radiotherapy regimen, chemotherapy regimen, treatment sequence, response to treatment, time to progression, relapse timing, relapse treatment, duration of survival, cause of death and treatment-related adverse events. Treatment-related toxicities were classified according to the Common Terminology Criteria for Adverse Events Version 5.0. Elevated bHCG and AFP cutoffs were determined by each institution.

Statistical Analysis

All data were summarized with standard descriptive statistics. Overall survival (OS) and corresponding 95% confidence intervals (CI) were calculated and presented using the Kaplan-Meier method. Comparison of survival curves was performed using Log-rank (Mantel-Cox) tests. P-values <0.05 were considered statistically significant. Statistical analyses were calculated and graphics designed using Prism 9 software (GraphPad, La Jolla, CA, USA).

RESULTS

Patient Characteristics

Demographics are summarized in Table 1 and clinical information in Table 2. A comprehensive review of the literature revealed 31 patients in 26 manuscripts from the years 1975 to 2021.[4,8-32] Most studies originated from East Asia (22/26). A review of tertiary institutions identified nine patients from five academic

institutions in the USA (Nationwide Children's Hospital, Columbus, OH; St. Jude Children's Research Hospital, Memphis, TN; Rady Children's Hospital, San Diego, CA; Children's Hospital Los Angeles, Los Angeles, CA; Massachusetts General Hospital, Boston, MA) and one patient from Brazil (Federal University of São Paulo, Vila Clementino, São Paulo, BR). Of the 41 total patients, mean age was 9.9 years (range, newborn to 35 years). The majority (90.2%) of patients were < 18 years of age. Age was unreported in one patient. A male predominance was noted (61%).

Sixteen patients had germinomas (39%), 16 had NGGCTs (39%) and eight had teratomas (19.5%); tumor histology was not reported for one patient. Of the NGGCTs, seven were YSTs (17%), two were embryonal carcinomas (4.9%), one was a STGC (2.4%), three were mixed GCTs (7.3%) and three were unspecified (7.3%). Of the teratomas, five were immature (12.2%), one was mature (2.4%) and two were unspecified (4.9%). Thirteen tumors were localized to the basal ganglia (31.7%), seven the posterior fossa (17%), three the pineal region (7.3%) and eight the sellar or suprasellar region (19.5%). Other tumors were localized to the third ventricle, fourth ventricle and cerebellopontine angle (CPA). Six patients (14.6%) presented with multiple intracranial lesions: basal ganglia/thalamus, basal ganglia/frontal lobe, pineal/suprasellar, pineal/CPA and ventral midbrain/CPA/pineal. Of these six patients, two had additional metastatic disease to the spine. One tumor was localized to the sellar region with spinal metastases.

Clinical Presentation and Tumor Markers

Presenting symptoms were reported for 33 patients (80.5%). Duration of symptoms was available for 18 patients (43.9%) and ranged from one week to 2.5 years (mean 6.9 months). Six of these patients (20%) had symptoms for greater than 6 months. Of the 33 patients whose presenting symptoms were reported, hemiparesis (24.4%) was the most common symptom, followed by visual disturbance (19.5%), nausea/vomiting (17%), lethargy (14.6%), headache (14.6%), polyuria (12.2%), ataxia (9.8%), motor impairment (9.8%), polydipsia (9.8%), head enlargement (7.3%), seizures (2.4%), amenorrhea (2.4%) and facial nerve palsy (2.4%); one tumor was identified on prenatal ultrasound.

Serum AFP and bHCG was tested in 25 and 28 patients, respectively. Of these patients, 14 (58.3%) had elevated serum AFP and 11 (39.3%) had elevated serum bHCG. Cerebrospinal fluid AFP and bHCG was tested in 14 and 12 patients, respectively. Of these patients, six (42.9%) had elevated CSF AFP and four (33.3%) had elevated CSF bHCG. In those with both serum and CSF testing, serum AFP matched CSF AFP in 11 of 12 patients (91.7%) while serum bHCG matched CSF bHCG in 9 of 10 patients (90%). Overall, 17 of 31 patients (54.8%) had elevated AFP, while 12 of 35 patients (34.3%) had elevated bHCG at initial diagnosis.

Treatment and Response

Treatment approaches are summarized in Table 3. Of the patients with germinomas (n=16), nine (56.3%) underwent surgical biopsy and seven (46.7%) underwent subtotal resection (STR). Ten patients (62.5%) received chemotherapy. All chemotherapies were platinum-based. Only one patient received chemotherapy alone. Of the patients who underwent combined chemotherapy/RT, all patients received chemotherapy prior to RT. Fourteen patients (87.5%) received RT; two patients (12.5%) received craniospinal irradiation (CSI) (mean 2370c Gy), three (18.8%) received whole brain radiotherapy (WBRT) (mean 29.3 Gy), four (25%) received whole ventricle irradiation (WVI) (mean 27 Gy), four (25%) received focal RT (mean 30 Gy) and one (6.3%) received an unspecified regimen. Four patients (25%) received primary site boost (mean total dose 43.3 Gy; three WVI, one CSI). Complete response (CR) was achieved in nine patients (56.3%) following therapy.

Of the patients with NGGCTs (n=16), five (31.3%) underwent surgical biopsy (three YSTs, one mixed GCT, one embryonal carcinoma), three (18.8%) underwent gross total resection (GTR) (two YSTs, one STGC) and four (25%) underwent STR (two YSTs, one embryonal carcinomas, one mixed GCT). Fifteen patients (93.4%) received chemotherapy; 10 (62.5%) received combined chemotherapy/RT (three YSTs, three mixed GCTs, one STGC, three unspecified) and four (25%) received chemotherapy-only (two YSTs, two embryonal carcinomas). All chemotherapies were platinum-based. One patient received no adjuvant therapy (one YST).

Ten patients (62.5%) received RT; four (25%) received CSI (mean 22.5 Gy), two (12.5%) received WBRT (mean 25.5 Gy), one (6.3%) received WVI (dose unreported), two (12.5%) received focal RT (mean 45.6 Gy) and one (6.3%) received an unspecified regimen. Three patients (18.8%) received primary site boost (mean total dose 27 Gy). Complete response was achieved in 12 patients (75%) following therapy.

Of the patients with teratomas (n=8), three (37.5%) underwent surgical biopsy-only (one immature teratoma, two unspecified teratomas) and five (62.5%) underwent GTR (four immature teratomas, one mature teratoma). Adjuvant therapy was chemotherapy-only (three immature teratomas) or RT-only (one unspecified teratoma). All chemotherapy regimens were platinum-based. Five patients (62.5%) achieved CR following therapy.

Treatment-Related Adverse Events

Treatment-related adverse events are summarized in Table 4. Sixteen patients (39%) experienced Grade 3-5 treatment-related complications. Grade 3-4 myelosuppression occurred in five patients. Nine patients experienced Grade 3-5 infections, which included four episodes of sepsis, three episodes of pneumonia, one episode of mucositis and one post-surgical infection of unknown origin. One patient experienced post-surgical cardiopulmonary failure and one experienced moyamoya following RT. Of the 16 patients, nine received combined chemotherapy/RT, four received chemotherapy only, one received RT only and two underwent surgery without adjuvant therapy. Of the 16 patients who experienced adverse events, eight (50%) died of their complications.

Outcomes

Time to follow-up was available for 32 patients (mean 3.9 years; range, one month to 21.2 years). Overall, nine patients (21.2%) experienced disease relapse or progression; four patients experienced local relapse after CR (one germinoma, one teratoma, two NGGCTs) and five patients experienced disease progression despite therapy. Of the four patients who experienced local relapse, salvage regimens included platinum-based chemotherapy (n=3), repeat surgery (n=2) and radiotherapy (n=1). Three patients who experienced disease relapse were successfully salvaged and had no evidence of disease (NED) at last follow-up, whereas one died from treatment-related pneumonia. Four patients who had progressive disease died, while one remained alive with residual tumor at last follow-up.

Overall, four patients (9.8%) died from tumor progression (three teratomas, one unspecified histology), while the remaining eight patients (19.5%) died from treatment-related adverse events. Of the germinoma patients, two died from chemotherapy-related sepsis, one from pneumonia, one from post-surgery cardiopulmonary failure and one from Moyamoya following RT only. Of the NGGCT patients, one died from chemotherapy-related sepsis, one from post-surgical infection and one from pneumonia following surgery/chemotherapy/RT.

At last follow-up, 28 patients (68.3%) were alive with NED and one patient (2.4%) was alive with residual tumor. The 3-year OS for all histological types was 66% (95% CI 45.7%-81.5%). Three-year OS was 62% for germinomas (95% CI 30.5%-85.5%), 79% for NGGCTs (95% CI 38%-94.3%) and 53% for teratomas (95% CI 13.2%-82.5%) (Fig. 1A). There was no significant difference in 3-year OS based on histology (p =0.74). Three-year OS was 74.7% (95% CI 47.4%-89.9%) for those who received RT, 76.7% (95% CI 48.2%-90.8%) for chemotherapy and 72.4% (95% CI 44.7%-90.5%) for combined chemotherapy/RT (Fig. 1b). There was no significant difference in 3-year OS based on treatment (p =0.87).

DISCUSSION

In 1998, Satge *et al.* reported that GCTs make up nearly a third of intracranial tumors in patients with DS, whereas they account for <4% in the general pediatric population.[3]Though a mechanism for this interaction is unestablished, DS is known to predispose to the development of gonadal GCTs through various mechanisms.[3] Few patients with DS and CNS GCTs have since been reported.[4] This study includes the largest reported cohort of patients with DS and CNS GCTs and provides insight into the characteristics, management and outcomes of this population.

Genetic and environmental differences influence the occurrence of CNS GCTs, as evidenced by differences in incidence by geographical location. Germ cell tumors account for <5% of all childhood CNS tumors in the United States, Germany and Canada.[33-35] In contrast, GCTs account for 2.1-9.4% in Japan and the Far East.[36,37] Race and ethnicity also play a role, as an analysis of the SEER database by Poynter *et al.* showed higher incidence rates of CNS GCTs in patients of Asian/Pacific Islander descent irrespective of gender, tumor location and histology.[38] Consistent with these findings, the majority of studies we identified in the literature (22/26) originated from Japan or China. Consistent with prior studies, CNS GCTs were also seen most frequently in male patients.[34] Male sex has been strongly associated with pineal involvement, whereas suprasellar involvement has been associated with female sex.[39,40]In our study, pineal localization showed a slight male predominance (5/9; 55.6%), whereas sellar/suprasellar involvement showed a female predominance (5/8; 62.5%). Overall, CNS GCTs in the general population most commonly occur in the pineal or suprasellar region.[1,36,37] Interestingly, the most common site of tumor involvement in our patients was the basal ganglia (13/41; 31.7%). Germ cell tumors arising in the basal ganglia or thalamus are relatively rare, representing only 5-10% of all primary intracranial GCTs.[41]

Comparable to prior studies, patients in our cohort displayed symptoms for an average of 6.9 months prior to diagnosis.[42] In a retrospective review of 30 patients with CNS GCTs, Crawford *et al* . reported a mean symptom duration of 8.4 months; symptoms including movement disorders, enuresis, anorexia, and psychiatric complaints led to delayed diagnosis (>6 months) in nine patients, whereas headache, nausea, vomiting and visual changes led to earlier diagnosis.[42] Similarly, patients in our cohort with symptoms >6 months had movement disorders (n=3) or polyuria/polydipsia (n=3) on presentation.

The Brain Tumor Registry of Japan reported a 5-year OS of 97% for patients with pure germinomas (n=200) from 2001 to 2004; within their database, germinomas made up 64% of all CNS GCTs.[37]In our study, germinomas accounted for 39% of all tumors and had a poor 3-year OS of 62%. Localized germinomas have historically been managed with WBRT/WVI followed by primary tumor boost, with CSI being reserved for disseminated germinomas.[43] More recently, chemotherapy has been incorporated to reduce the late adverse-effects caused by RT.[44,45] In an analysis of the SIOP-CNS-GCT-II trial, Calaminus *et al.* showed that following CR to induction chemotherapy, patients with localized germinomas (n=58) who received 24 Gy WVI without a tumor boost had a 4-year event-free survival of 98%.[45] Furthermore, Bartels *et al.*demonstrated that 18 Gy WVI with 12 Gy tumor boost was associated with an excellent 3-year progression-free survival rate of 94.5.[44] In our cohort, most germinoma patients received RT or combined chemotherapy/RT.

In contrast to germinomas, NGGCTs are less common and associated with worse outcomes.[46] In an analysis of the European SIOP-CNS-GCT-96 trial by Calaminus *et al.* , 5-year OS for patients with localized NGGCTs (n =116) was 82%.[46] More recent trials have shown better outcomes – In a phase II trial for patients with newly-diagnosed NGGCTs, Goldman *et al.* demonstrated a 5-year OS of 93% when neoadjuvant chemotherapy was followed by 36 Gy CSI with 54 Gy tumor-bed boost. In comparison, Fangusaro *et al.*showed that reduced RT (30.6 Gy WVI and 54 Gy tumor-bed boost) resulted in a similar OS of 92.4% at 3 years, though it is important to note that all patients who had treatment failure were in the spine.[47] In our cohort, 3-year OS for NGGCTs was 79%.

The mainstay of treatment for teratomas is maximal surgical resection, while adjuvant chemotherapy and RT is recommended for some patients depending on each case and residual disease.[43] Huang*et al.* reported a 5-year OS of 40% in 13 immature teratoma patients treated with maximal possible resection, and no difference in outcomes were found between patients who received chemotherapy and/or RT versus those who did not.[48] Three-year OS for teratomas (five immature, one mature, two unspecified) in the present study was comparable at 53%; notably, all three patients who underwent biopsy-only died from tumor progression within one year, whereas all four patients who underwent GTR were alive at follow-up.

The SIOP-96 trial reported grade 3-4 toxicities in 27/83 patients (33%) receiving combined chemotherapy/RT and 26/154 patients (17%) receiving RT only; there were no treatment-related deaths.[49] In contrast, while 16/41 patients (39%) in the present study experienced grade 3-4 toxicities, 50% died from their toxicity (n=8). Moreover, five of the 16 germinoma patients (31%) died from treatment-related toxicity, which resulted in a

poor 3-year OS of 62%. Trisomy-21 is associated with functional deficiencies in B-cell, T-cell and phagocytic cell systems, resulting in an increased risk of developing and succumbing to various infectious diseases.[5,7] In an analysis of the AML-BGM-93 trial for AML, Lehrnbecher *et al.*found that patients with DS had significantly higher rates of infection-associated fatal complications (5/28; 17.9%) than children without DS (15/276; 5.4%).[5] Notably, infection-related mortality significantly decreased in the subsequent AML-BFM 2004 trial (3/61; 4.9%), in which a reduced-intensity chemotherapy regimen was utilized.[7]

Craniofacial abnormalities, increased secretions and hypotonia associated with DS contribute to higher rates of upper-airway obstruction, particularly after the induction of anesthesia.[50] After tonsillectomy or adenoidectomy surgeries, Goldstein *et al.* found that children with DS more frequently required airway management or observation in the pediatric intensive care unit compared to controls (25% *versus*0%).[50] Finally, patients with DS are at a particular risk of developing Moyamoya due to cranial RT, potentially because several proteins encoded on chromosome 21 including superoxide dismutase 1, interferon gamma receptor and cystathionine beta-synthase affect arterial physiology as well as DNA repair.[6]

Our study has multiple limitations; despite being the largest cohort of patients with DS and CNS GCTs, the small number of patients limits our conclusions regarding treatment approach. Moreover, our reliance on multiple institutions limits the consistency of pathology or radiology reports, as well as tumor marker levels. The inconsistency of data reporting by previously published studies also limits the thoroughness of our retrospective cohort.

CONCLUSIONS

Patients with DS treated for CNS GCTs are at an increased risk of treatment-related death, particularly from treatment-related infection. Based on our experience, we suggest that a different therapeutic approach may be considered for this patient population in which treatment intensity is reduced. To evaluate the long-term effects of RT and chemotherapy in these patients, longer follow-up is needed. An expanded multi-institutional analysis is warranted, as well as subgroup specific analysis for DS patients within prospective clinical trials of CNS GCTs.

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Statements and Declarations : The authors do not have any conflicts of interest to disclose. No funding was used to support this work. The authors have no financial interests to disclose. All authors contributed to the study conception and design. Material preparation, data collection and analysis was performed by Micah K. Harris and Mohamed S. Abdelbaki. The first draft of the manuscript was written by Micah K. Harris, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Sharing: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Figure Legends

Fig 1 (A) Overall survival (OS) probability according to tumor histology. OS was defined as time from diagnosis to death or censoring. Log-rank test showed a p -value of 0.74. (B) OS probability according to primary treatment. Log-rank test showed a p -value of 0.87 Abbreviations: NGGCT, non-germinomatous germ cell tumor

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