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Treatment barriers and clinical outcome of children with medulloblastoma in China: a report from the Chinese Children's Cancer Group (CCCG)

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Abstract

Background. Medulloblastoma (MB) is the most common malignant central nervous system tumor of childhood. Management requires interdisciplinary care and is associated with unique challenges in developing regions. Here, we report the characteristics, clinical outcome and treatment barriers for Chinese children with MB based on a multi-institutional cohort from the Chinese Children's Cancer Group (CCCG).

Methods. Retrospective cohort study among 12 Chinese pediatric oncology units from the CCCG Brain Tumor Workgroup on patients aged <18 years diagnosed with MB from 2016 to 2019.

Results. 221 patients (male:female = 138:83) were included, 175 (79%) were ≥3 years of age, and 46 (21%) <3 years. 177 patients (80%) were completely staged, among which 50 (28%) had metastasis and 70 (40%) were considered to have high-risk (HR) disease. Gross/near-total resection was achieved in 203 patients (92%). In patients where molecular grouping could be assigned, 19 (16%), 35 (29%), and 65 (54%), respectively had WNT-activated, SHH-activated, and Group 3/4 MB. The median duration between resection and initiation of adjuvant therapy was 36 days. Respective 2-year PFS and OS rates were 76.0 ± 3.0% and 88.0 ± 2.3%. PFS was significantly associated with age, metastatic status and clinical risk grouping. Chemotherapy use during CSI or alkylator choice were not significant predictors for patient outcome.

Conclusions. We reported the clinical profiles and outcome from the largest cohort of Chinese children with MB after multi-modal therapy. Strengths and limitations on the local provision of neuro-oncology service are identified.

Key Points

- We reported the characteristics and outcome of 221 Chinese children with medulloblastoma based on the CCCG experience.
- Unique challenges and opportunities for enhancing the delivery of pediatric neuro-oncology service in China are described.

Importance of the Study

Management of childhood medulloblastoma requires interdisciplinary input and is associated with unique challenges in low and middle income countries. We described the largest reported cohort of Chinese patients (n = 221) with medulloblastoma based on the Chinese Children's Cancer Group experience between 2016 and 2019, focusing on the current status of care, short-term outcome, and system barriers in the delivery of pediatric neuro-oncology service. While we observe a high rate of complete tumor removal, reasonable survival at 2 years, and feasibility of molecular grouping, we also acknowledge the incomplete disease staging in 20% of patients, inadequate risk-stratification, lack of standardization in protocols, and at times, shortage of key chemotherapeutic agents. Our study depicted the hurdles and potential opportunities for pediatric brain tumor care in China.

Approximately 10,000 children are diagnosed with central nervous system (CNS) tumors in China each year.[1,2] Despite the advances in socioeconomic status and level of medical care in the country,[3] delivery of pediatric neuro-oncology service faces unique challenges.[2,4,5]The inadequate interdisciplinary collaboration and unavailability of local therapeutic guidelines hinders the standardization of treatment, while limitation of drug access complicates the application of protocols adopted from international collaborative groups. Compared to pediatric hemic malignancies, childhood brain tumors are associated with relatively grim prognosis as well as complex and costly evaluation procedures, contributing to treatment abandonment and loss of follow-up.[6,7]

As the most common malignant pediatric CNS tumor, medulloblastoma (MB) is a prototypical entity in pediatric neuro-oncology studies.[8,9] These patients require multimodal therapy for cure, whereas clinical risk-stratification allows cytotoxic therapy to be delivered in a dose-adapted manner ensuring quality survival. Furthermore, recent understanding of the biologic underpinnings in MB has refined diagnostics and our ability to devise novel therapeutic strategies. In spite of the population size, literature on the outcome of Chinese children with MB is scarce.[7,10–16] Reports are mostly restricted to experience from individual neurosurgical units, limiting the description on referral pathways, adjuvant treatment, and disease course after interdisciplinary care. More comprehensive and granular study on the current pattern of care and clinical outcome based on a more representative cohort from China is needed. Herein, we report the clinical features, management and short-term outcome of more than 200 children with MB treated in hospitals of the Chinese Children's Cancer Group (CCCG) network between 2016 and 2019.

Methods

Study Design and Cohort

This is a multi-institutional retrospective cohort study among 12 Chinese pediatric oncology units from the CCCG Brain Tumor Workgroup, comprising tertiary referral centers from Guangzhou, Shanghai, Beijing, Shenzhen, Hong

Kong, Hebei and Henan. Patients under the age of 18 years diagnosed with MB between January 2016 and December 2019 were included, encompassing patients who presented to our centers (~80%) or were referred after initial resection (~20%). Data on demographics, clinical features, disease stage (according to Chang *et al.*[17]), surgical and adjuvant therapy, and outcome were curated. Patient status as of the latest evaluation on or before March 31, 2021 was reported. Histologic and imaging interpretations were based on the reports of pathologists and radiologists at individual institutions. The study was approved by Institutional Review Boards of the participating institutions.

Treatment Approach and Study Definitions

Patient management was not standardized among institutions, but was mostly referenced against the age and risk-stratified national consensus guideline (CCCG-MB-2017) on managing childhood MB conceptualized in 2016 (Supplementary Figure 1).[18] Specifically, patients diagnosed ≥3 years of age were considered as having average-risk (AR) disease when gross or near-total resection (GTR/NTR) was achieved (≤1.5 cm^2 residual), disease was localized (M0), and if available, histology subtype being nonlarge cell/anaplastic (LCA), other patients were considered as having high-risk (HR) disease. Risk-adapted craniospinal irradiation (CSI) with local boost and concurrent vincristine, followed by alkylator and platinum-based adjuvant chemotherapy was recommended.[19] Infants and younger children < age of 3 were considered as having AR disease when GTR/NTR was achieved, disease was localized, and histology subtype was nodular/desmoplastic or extensive nodular (MBEN), and otherwise as having HR disease. Recommended therapy for these younger patients was chemotherapy for radiation deferral or avoidance. In patients who underwent complete imaging and cytologic staging, risk groups were retrospectively assigned for all patients in this study according to the aforementioned criteria.

Molecular Studies

A subset of patients underwent molecular profiling of tumor tissue. Molecular classification was based on targeted mutational and chromosomal copy-number variant (CNV) analysis (Genetron Health, China, $n = 88$), NanoString (n = 19, algorithm according to Northcott *et al.*),[20] or genome-wide DNA methylation profiling (German Cancer Research Center Classifier, n = 14).[21] For mutational/CNV-based analysis, tumors were classified into WNT-activated, SHH-activated, and Group 3/4 MB. Molecular groups were not taken into account for risk-stratification.

Statistical Analyses

Date of diagnosis was defined as the date of first resection/biopsy. Survival analyses was performed using the Kaplan–Meier method, with progression-free survival (PFS) defined as the duration between the dates of diagnosis and date of progression, death from any cause, or last follow-up (censored), and overall survival (OS) defined as the duration between the dates of diagnosis and death from any cause. Patient survival was compared based on potential prognostic factors including age at diagnosis (< vs ≥ 3 years), sex, metastatic status, extent of resection (GTR/NTR vs subtotal resection/biopsy [STR/Bx]), risk groups (AR vs HR for patients with complete staging only, and for all patients where those with incomplete staging were considered as having HR disease), histologic subtypes, time to initiation of adjuvant therapy (≤ vs > median) and molecular groups using the log-rank test. P-values <.05 were considered significant. All analyses were performed by using R version 4.03.

Results

Demographics and Clinical Characteristics

During the study period, 225 patients were diagnosed with MB. After excluding four patients, namely, one who was still on treatment, and three who abandoned treatment, 221 remained for analysis (Table 1). The median age of diagnosis was 6.4 years (range: 0.5–16.7), with 175 patients (79%) diagnosed ≥3 years of age, and 46 patients (21%) <3 years. The male to female ratio was 138 to 83 (62%:38%). At diagnosis, 212 patients (96%) underwent MRI of the spine and 183 patients (83%) had cerebrospinal fluid (CSF) cytologic study, with 177 patients (80%) completely staged. Among those who were completely staged, 127 patients (72%) had localized (M0) disease, while metastasis (M+) was present in 50 (28%, M1 = 7, M2 = 9, M3 = 32, M4 = 2). For patients who were not completely staged, evidence of metastasis was present in 11 patients (M1 = 1, M2 = 5, M3 = 5) based the available evaluation. Thus, a total of 61 patients in the entire cohort had evidence of metastasis, 127 patients had confirmed M0 disease after complete staging, and 33 patients had no evidence of metastasis but staging was incomplete.

Histologic and Molecular Evaluation

Histologic subtypes were classic in 137 (62%), nodular/desmoplastic in 34 (15%), MBEN in 5 (2%), LCA in 15 (7%), and not reported in 30 (14%). Molecular grouping performed for 121 patients revealed 19 (16%), 35 (29%), and 65 (54%) tumors being assigned to WNT, SHH, and Group 3/4 disease respectively (molecular group could not be assigned in 2). Demographic and clinical features of patients by molecular group are summarized in Table 2. When restricted to studies using NanoString or methylation array (n = 33), molecular group assignments were WNT in 5 patients (15%), SHH in 10 (30%), Group 3 in 6 (18%), and Group 4 in 12 (36%).

Treatment Characteristics

Extent of resection was GTR in 190 (86%) patients, NTR in 13 (6%) and STR/Bx in 18 (8%). Forty-eight (22%) patients required ventriculo-peritoneal shunting. Posterior fossa syndrome was encountered in 18/221 patients (8%). Among the patients who were completely staged (n = 177),

Table 1. Clinical, molecular and treatment characteristics of the entire treatment cohort and stratified by age

	All *N* = 221	N	<3 y *N* = 46	≥3 y *N* = 175	*P* value
Age of diagnosis, median (range), y	6.4 (0.5–16.7)	221	2.0 (0.5–3.0)	7.3 (3.1–16.7)	<0.001
Sex		221			0.79
Female	83 (37.6%)		16 (34.8%)	67 (38.3%)	
Male	138 (62.4%)		30 (65.2%)	108 (61.7%)	
Extent of disease		188			0.04
M+	61 (32.4%)		20 (46.5%)	41 (28.3%)	
M0	127 (67.6%)		23 (53.5%)	104 (71.7%)	
Histologic subtype		221			0.004
Classic	137 (62.0%)		23 (50.0%)	114 (65.1%)	
Nodular/desmoplastic	34 (15.4%)		14 (30.4%)	20 (11.4%)	
Extensive nodularity	5 (2.3%)		3 (6.5%)	2 (1.1%)	
Large cell/anaplastic	15 (6.8%)		1 (2.2%)	14 (8.0%)	
Not available	30 (13.6%)		5 (10.9%)	25 (14.3%)	
Molecular group		121			<0.001
WNT	19 (15.7%)		0	19 (21.1%)	
SHH	35 (28.9%)		17 (54.8%)	18 (20.0%)	
Group 3 or 4	65 (53.8%)		12 (38.7%)	53 (58.9%)	
MB, NOS	2 (1.7%)		2 (6.5%)	0	
Staging evaluation		221			.79
Complete	177 (80.1%)		38 (82.6%)	139 (79.4%)	
Incomplete	44 (19.9%)		8 (17.4%)	36 (20.6%)	
Treatment approach		221			<.001
Chemo only	27 (12.2%)		26 (56.5%)	1 (0.6%)	
Chemo->CSI	10 (4.5%)		8 (17.4%)	2 (1.1%)	
Chemo->CSI->chemo	21 (9.5%)		4 (8.7%)	17 (9.7%)	
CSI	2 (0.9%)		0	2 (1.1%)	
CSI->chemo	159 (71.9%)		7 (15.2%)	152 (86.9%)	
Focal RT->chemo	1 (0.5%)		0	1 (0.6%)	
No adjuvant	1 (0.5%)		1 (2.2%)	0	
Extent of surgery		221			.82
GTR	190 (86.0%)		39 (84.8%)	151 (86.3%)	
STR	18 (8.1%)		4 (8.7%)	14 (8.0%)	
NTR	13 (5.9%)		3 (6.5%)	10 (5.7%)	

107 patients (60%) were retrospectively assigned to have AR disease, and 70 (40%) to have HR disease.

The median duration between surgical resection and initiation of adjuvant therapy was 36 days (range: 12–113, Supplementary Figure 2A). For patients aged ≥3 years (n = 175), CSI with local boost was given in 173 patients (one received focal irradiation, one received chemotherapy only); 154 patients had CSI following surgery (median duration between surgery and CSI: 37.5 days, range: 14–107, Supplementary Figure 2B), while 19 patients received chemotherapy (median: 2 cycles, range: 1–8) before CSI was given.The median CSI doses for completely-staged patients with AR (n = 95) and HR (n = 42) disease were 30 Gy (n = 95, range: 23.4 - 38.4, 38 patients ≥ 36Gy; tumor total median 54 Gy) and 36 Gy (n = 39, range: 23.4–40; tumor total median 54 Gy) respectively. Concurrent chemotherapy during CSI was delivered in 59 of 163 patients (vincristine = 48, vincristine and carboplatin = 8, temozolomide = 3) where information was available (missing in 10). Other than two patients who received CSI only, other patients ≥3 years (n = 173) received adjuvant chemotherapy with alkylator and platinum based "Packer" regimens (median: 8 cycles, range: 1–11).[19] The alkylator of choice was cyclophosphamide in 60, lomustine in 52, semustine in 31, a combination in 22, and not reported in eight. While the majority of patients received cisplatin, two received nedaplatin; and

Table 2. Clinical features of patients when stratified by molecular groups

	WNT	SHH	Group 3/4	*P* value
	N = 19/119* (16%)	*N* = 35/119 (29%)	*N* = 65/119 (55%)	
Age of diagnosis, median (range), y	9.4 (4.3–14.8)	3.3 (0.8–12.9)	6.4 (1.3–16.7)	<.001
Age of diagnosis				<.001
<3 y	0	17 (48.6%)	12 (18.5%)	
≥3 y	19 (100%)	18 (51.4%)	53 (81.5%)	
Sex				.015
Female	12 (63.2%)	11 (31.4%)	18 (27.7%)	
Male	7 (36.8%)	24 (68.6%)	47 (72.3%)	
Extent of disease				.20
M+	2 (12.5%)	10 (38.5%)	18 (32.7%)	
M0	14 (87.5%)	16 (61.5%)	37 (67.3%)	
Histologic subtype				<.001
Classic	15 (78.9%)	14 (40.0%)	51 (78.5%)	
Nodular/desmoplastic	0	16 (45.7%)	2 (3.08%)	
MBEN	0	1 (2.9%)	0 (0.00%)	
Large cell/anaplastic	1 (5.3%)	1 (2.9%)	5 (7.69%)	
Not specified	3 (15.8%)	3 (8.6%)	7 (10.8%)	

* Two patients where molecular grouping could not be assigned excluded.

although vincristine was the vinca alkaloid of choice, the drug was replaced by vindesine in 11.

For patients aged <3 years (n = 46), 26 received chemotherapy only, 19 received a combination of chemotherapy and radiation, all in the form of CSI and local boost (CSI dosage median: 35 Gy, range: 23.4–36; tumor total median 54 Gy), and one died of herniation post-operatively before start of adjuvant therapy. CSI was given in a deferred manner after chemotherapy in 12 (in view of young age), whereas in 7, it was given after tumor resection. The median age for starting CSI in these 19 patients was 2.8 years (range: 2.1–3.2). The chemotherapeutic approach adopted was heterogeneous, and was based on the CCCG-MB-2017 protocol for infants (cyclophosphamide/vincristine, high-dose methotrexate, carboplatin/etoposide) in 35, the "Packer" regimen in 7, and the HeadStart strategy in 3. The median number of adjuvant chemotherapy cycles was 12 (range: 3–16).

Survival, Prognostic Factors, and Adverse Effects

Median follow-up of our cohort was 2.4 years (range: 0.1–5.1), during which 59 progressions and 30 deaths were observed. The causes of death were disease progression in 28, sepsis in one and herniation in one. The 2-year PFS and OS rates for the entire study cohort were 76.1 ± 2.9% and 88.0 ± 2.3% respectively, with 3-year PFS and OS being 71.5 ± 3.3% and 85.6 ± 2.6% (Figure 1).

Among the 177 patients who were completely staged, 16 progressions and 9 deaths occurred in patients who were considered as having AR disease (n = 107), while 29 progressions and 17 deaths occurred in those with HR disease (70). Respective 2-year PFS for patients ≥3 years with AR disease, ≥3 years with HR disease and <3 years (all risks) were 91.3 ± 3.0%, 68.2 ± 7.4%, and 52.1 ± 7.4%. Two-year PFS for patients ≥3 years with AR disease who received 23.4Gy CSI was 90.2 ± 5.5%.

PFS was significantly associated with age (P < .0001), metastatic status (patients with complete staging and those with M+ disease despite incomplete staging, P = .028), risk group for completely staged patients (P < .0001, ≥3 y P = .010, <3y P = .16), risk group for all patients (assuming that incompletely staged patients have HR disease, P < .0001), but not sex (P = .55), extent of resection (P = .20), histologic subtype (P = .99), or time to initiation of adjuvant therapy (P = .51). By molecular groups, patients with WNT-activated disease had a trend towards better outcome compared with Group 3/4 tumors, which appeared to have an intermediate outcome, and SHH-activated disease, which carried a trend towards inferior outcome (P = .10). In patients ≥3 years of age, concurrent chemotherapy during radiotherapy was not significantly associated with difference in PFS (P = .65, Figure 2), even when these patients were further stratified by risk groups in those completely staged (AR P = 0.16, HR P = .98); the choice of alkylator did not impact PFS (patients who received mixed agents excluded, P = .75).

Documentation of adverse effects from adjuvant treatment was limited. Among the 93 patients where auditory evaluation (pure-tone audiometry or age-appropriate behavioral hearing test) was performed on follow-up, 17 (18%) reported abnormal test findings. Lethal septic complication was reported in one patient (as mentioned

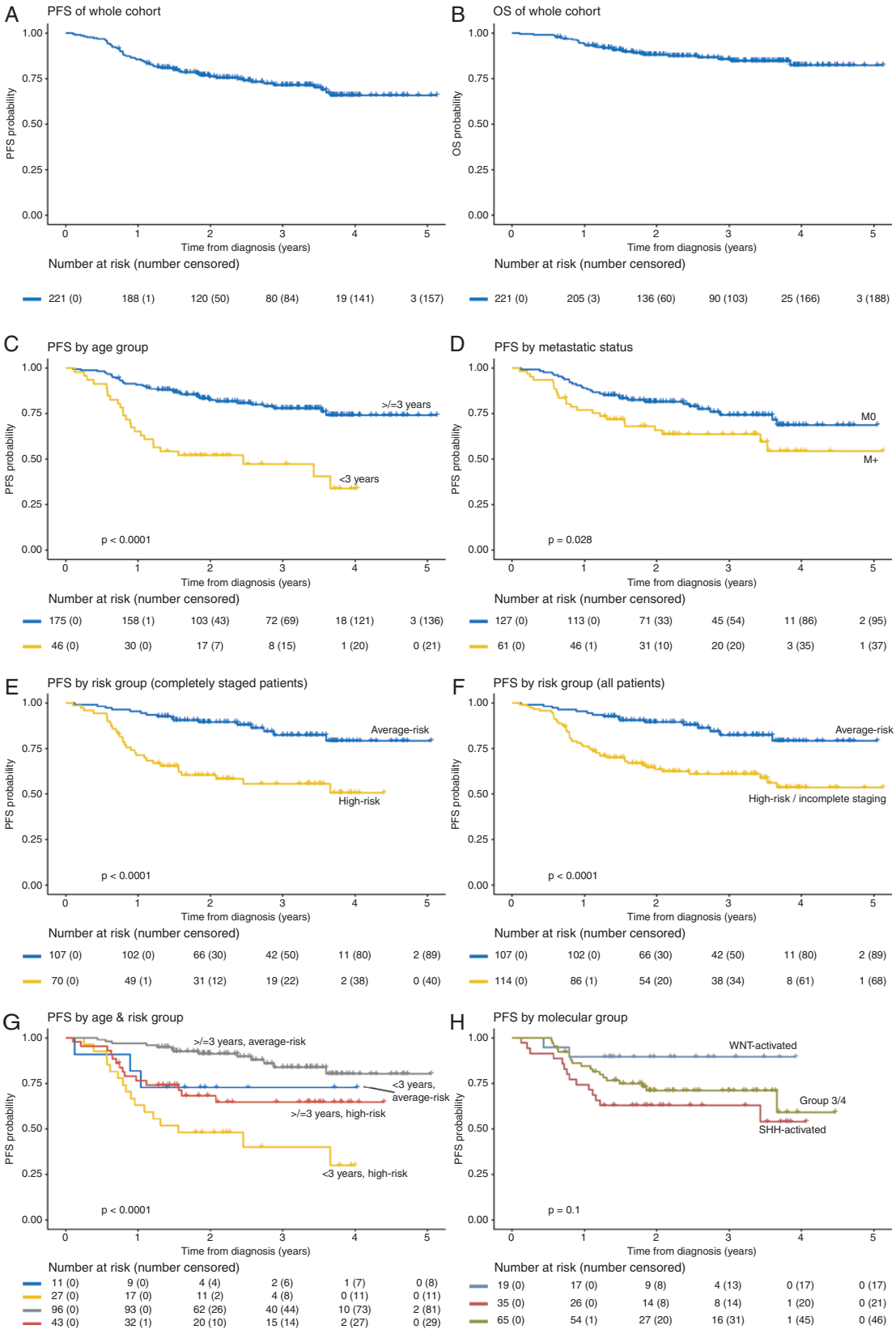

Figure 1. (A, B) Progression-free survival (PFS, missing data from one patient) and overall survival (OS) of the entire study cohort. PFS by (C) age, (D) metastatic status (completely staged patients and patients with M+ disease despite incomplete staging), (E) risk group (patients with complete staging), (F) risk group (all patients, with incompletely staged patients assigned to the HR group) (G) age and risk group, (H) molecular group.

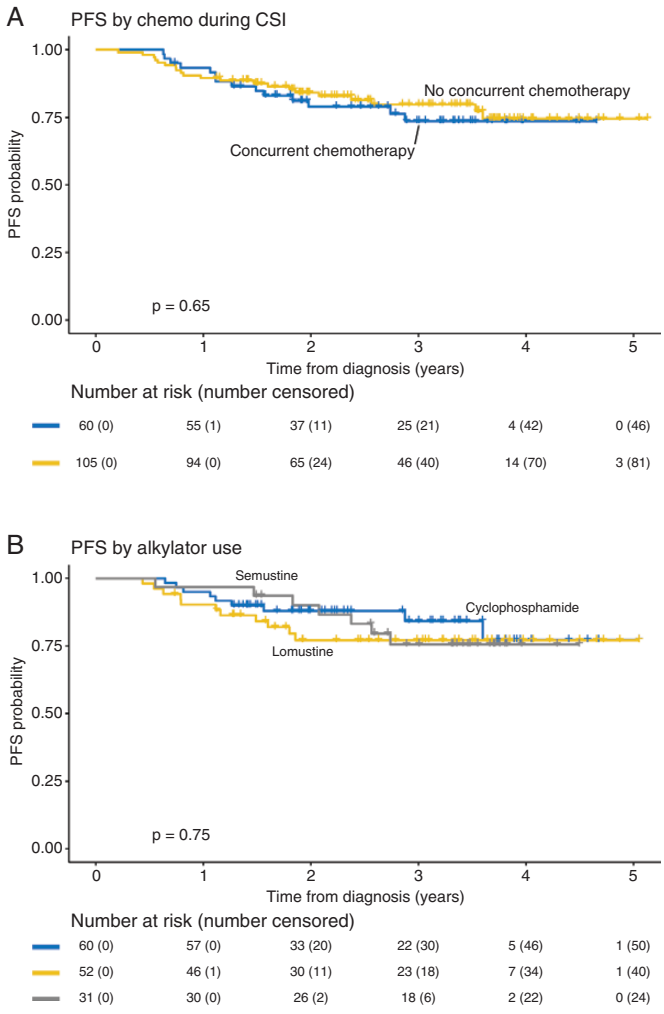

Figure 2. Progression-free survival (PFS) in patients ≥3 years by (A) chemotherapy use during CSI and (B) choice of alkylator.

above). Two patients with Li-Fraumeni syndrome and SHH-activated MB developed therapy-related myelodysplastic syndrome.[22]

Discussion

Here, we provide real-world data on the management of children with MB in China, where one-fifth of the world's population resides. The optimal treatment for MB relies on maximal safe resection followed by timely irradiation and chemotherapy in an age and risk-stratified manner, necessitating close interdisciplinary collaboration. In China, institutions equipped with all the specialties required to provide holistic care for pediatric brain tumor patients are rare, prompting the need for inter-hospital referrals and in turn relies on panicking families to navigate the system. Whilst prior reports from China mostly represent piecemeal description of institutional-based experience, our study demonstrates the feasibility of coordinated neuro-oncology care to be delivered among tertiary referral centers in major cities of the country.[7,10–16] The available neurosurgical expertise resulted in total or near-total tumor removal in more than 90% of patients. This is followed by complete staging evaluation in 80%, as well as initiation of adjuvant therapy at an average of five weeks after operation. The 2-year PFS at 76% for the entire cohort, and the age and risk-stratified PFS at 2 years (≥3 y AR disease, ≥3 y HR disease, <3 y) are comparable to landmark historical data that included pediatric patients with various ages and risk features.[23] In particular, the 90% 2-year PFS for children ≥3 years with AR disease receiving 23.4 Gy CSI is similar to results from the Children's Oncology Group A9961 study which offered the backbone for formulation of the CCCG-MB-2017 guideline.[19] The 2-year PFS of 52% for children <3 years compared favorably with results from the SJYC07 study (2-y PFS ~35%), this however is achieved in the context of CSI being given to 41% of these young children as part of the upfront treatment, a practice that deviates from our national guideline and current international standard of care. Introducing CSI-sparing strategies

based on the use of intraventricular methotrexate, or high-dose chemotherapy with autologous stem cell rescue in a molecularly-stratified manner would facilitate the enhancement of outcome and mitigation of treatment-related toxicities in young children with MB in China.[24–26] Further efforts should ensure disease staging, in particular CSF sampling, to be completed in all patients without contra-indications.[27] This would be crucial for informing CSI dose-stratification, and its implementation requires education of pediatric oncologists, as well as radiation oncologists and neurosurgeons who in many cases are the main healthcare providers prior to referral for maintenance chemotherapy. The timeliness of adjuvant therapy should also be emphasized in view of the negative impact of delayed treatment initiation in MB.[28–30] In lieu of relying on patient families to research on the available treatment institution, arrange specialist consultations and convey medication information, formal referral and liaison at the healthcare provider level should be the norm and could be facilitated by a national pediatric oncology network such as the CCCG.

Additional hurdles are apparent for pediatric MB management in the region. Despite the availability of local treatment guideline, the therapeutic strategies are far from being standardized. In older children, the ability to adopt reduced CSI dosing is an established approach to minimize long-term toxicities in patients without risk features.[19] Nonetheless, 40% of children ≥3 years who were considered to have AR disease in our study received ≥36 Gy CSI, reflecting a radiation oncology practice that is influenced by the fear for undertreating patients and potential medicolegal repercussions, lack of confidence with regards to reports on postoperative imaging regarding residual disease, and adult-based protocols where dose-stratification is typical not incorporated. This highlights the need for further reinforcement of the current evidence through structured cross-disciplinary training.[31] Moreover, the variation in practice among centers reflects practical restrictions on service delivery. For the choice of chemotherapeutic agents, lomustine is often unavailable in mainland China and when available, increasingly costly; cyclophosphamide, while proven to be equally effective and widely being adopted in MB protocols, requires additional in-patient days when compared with oral alkylating agents. As a result, semustine, a 4-methyl derivative of lomustine, is commonly used as a replacement. Despite the lack of comparative trials on the efficacy among these agents, we did not observe a different in PFS according to choice of alkylator in our cohort. Similarly, only one-third of patients who received CSI were given concurrent chemotherapy. This is contributed by the lack of pediatric oncologic input before the initiation of radiotherapy, vincristine shortage which is not uncommon (often replaced with vindesine for maintenance), and concerns for peripheral neuropathy developing during the subsequent course of treatment. Despite that vincristine during CSI have been adopted as a standard practice, evidence supporting its benefit versus CSI alone is lacking. In fact, successive trials led by St. Jude Children's Research Hospital had not incorporated concomitant chemotherapy during CSI.[32,33] The current practice of vincristine use during CSI regardless of risk and subgroup should be scrutinized in future MB studies. Beyond tumor-directed therapy, protocols for monitoring of acute and long-term treatment toxicities are direly needed as evidenced by the lack of structured surveillance and thus data on chronic health deficits, such as neurocognitive impairment, in our study.[34] Indeed, only less than half of the cohort received hearing evaluation at some point of their follow-up, while the incidence of posterior fossa syndrome reported (8%) is lower than that described in the literature (10–40%) strongly suggesting a degree of under-reporting.[35] Tumor and therapy related side effects are frequent in survivors in pediatric brain tumors and a systematic approach to detect these morbidities early is essential for estimation of their burden in Chinese patients and to secure resources for supportive interventions. Only with such comprehensive approach would children with MB from the country be surviving with satisfactory quality of life.

The identification of molecular groups within MB has revolutionized our understanding of its biology, informed ongoing trial designs and guided search for therapeutic targets. Our experience indicates that "omic" platforms are increasingly accessible to physicians and patient families in China as commercially-available, patient-financed tests. Catered towards adult-onset cancer types where mutational burden is high, panel or exome-sequencing are offered by third-party laboratories with classification algorithms for MB subgroups devised based on driver mutations and CNVs, rather than the established transcriptomic and epigenomic approaches. While the identification of pathogenic alterations in the WNT and SHH pathways might allow confident assignment of tumor groups for WNT-activated and SHH-activated MBs, the delineation between Group 3 and Group 4 tumors is frequently impossible and poses great concerns in case molecular grouping is to be used for risk-stratification in future protocols. In line with the upcoming WHO CNS tumor classification recommendations, we advocate for genome-wide DNA methylation profiling as the method of choice in assigning molecular groups for medulloblastoma and other pediatric CNS tumors.

We acknowledge that there are a limitations to our study. First, the participating institutions represent leading pediatric oncology units within the country. Thus our observations involve referral bias and could not be extrapolated to patients being managed in regional medical centers, nor could we claim that the current outcome represents a population-wide data from China where hundreds of children are diagnosed with medulloblastoma each year. Nonetheless, we aim to demonstrate feasibility of collaborative studies among the more established centers in China and at the same time, to highlight shortcomings in these units that represent the expertise available locally. With the rarity of pediatric brain tumors, centralization of care is preferred and the study institutions should serve as centers of excellence to support regional centers through establishing effective referral pathways.[36] Second, central imaging and histopathologic review have not been carried out. In spite of the additional resources required, this represents an essential component that has to be incorporated into upcoming prospective, multi-centered studies in China to avoid inter-observer variability and might be facilitated by increasingly available Cloud-based data transfer and digital pathology. Third, the duration of follow-up in our cohort is modest, allowing us to focus only

on short-term progression-free survival with regards to patient outcome. Lastly, the retrospective study design did not allow therapeutic approaches and techniques of evaluation to be harmonized. The latter includes more detailed histopathologic and molecular evaluations, such as analysis for *TP53* mutational status in SHH tumors and *MYC/MYCN* amplification in Group 3/4 disease. This however allowed us to explore the current variations in practice, and to perform hypothesis-generating comparisons, which could form the basis for research questions in future prospective protocols. Overall, the CCCG Institutions should serve as the driving force to consolidate the local pediatric neuro-oncology referral network, and to standardize diagnostic and therapeutic strategies through multi-center clinical trials.

Conclusions

In conclusion, we summarized the clinical profiles and outcome after multi-modal therapy from the largest reported multi-insitutional cohort of Chinese children with MB. Strengths and weaknesses in the system on the provision of neuro-oncology service are identified. This sets the stage for protocolizing the care for children with MB in China and offers data for upcoming interventional studies to benchmark against.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Advances* online.

Keywords

children | China | collaborative group | medulloblastoma | multidisciplinary

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Data Availability

All data generated or analyzed during this study are included in this published article.

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