REVIEW

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Challenges and opportunities for managing pediatric central nervous system tumors in China

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Funding source
American Lebanese Syrian Associated Charities

Received: 12 August, 2020
Accepted: 30 August, 2020

ABSTRACT
Central nervous system (CNS) tumors represent the most deadly cancer in pediatric age group. In China, thousands of children are diagnosed with CNS tumors every year. Despite the improving socioeconomic status and availability of medical expertise within the country, unique challenges remain for the delivery of pediatric neuro-oncology service. In this review, we discuss the existing hurdles for improving the outcome of children with CNS tumors in China. Need for precise disease burden estimation, lack of intra- and inter-hospital collaborative networks, high probability of treatment abandonment, along with financial toxicities from treatment represent the key challenges that Chinese healthcare providers encounter. The tremendous opportunities for advancing the status of pediatric neuro-oncology care in and beyond the country are explored.

KEYWORDS
Pediatric cancer, Central nervous system tumor, China, Multi-disciplinary team, Collaboration

DOI: 10.1002/ped4.12212

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Introduction

Cancer is an emerging global priority in child and adolescent health.[1-3] Eighty percent of this burden is born by low- and middle-income countries (LMICs), where unique challenges exist.[1,2,4,5] As the most populous country in the world, China has a pediatric population (<18 years) of 271 million, and approximately 45 000 new childhood cancers are diagnosed each year.[5,6] Over the past two decades, the treatment for acute lymphoblastic leukemia (ALL)—the most frequent childhood cancer—has evolved from inadequate to state-of-the-art under national collaborative trials enrolling up to 2000 patients per year.[7,8] Such progress was achieved through perseverance and joint efforts among clinicians, researchers, policy makers, international partners, pharmaceutical companies, philanthropic foundations, and patient advocates. More recently, there is a growing attention to the needs for children with solid tumors, which make up two-thirds of pediatric cancer cases. Central nervous system (CNS) tumors are the most common pediatric solid tumor and have the highest mortality rate among all childhood cancers.[9] The management of pediatric CNS tumors, such as medulloblastoma (MB), glioma, ependymoma, and germ cell tumors, necessitates timely interdisciplinary input from neurosurgeons, radiation oncologists, pediatric oncologists, radiologists, and pathologists.[10,11] The heterogeneity of CNS tumors and rapid advances in our understanding of disease biology complicate efforts to estimate their incidence and formulate standard-of-care guidelines.[12] Children with CNS tumors in China encounter further struggles specific to their local contexts. Here, we review the ongoing challenges for delivering pediatric neuro-oncology care in China and highlight the unique opportunities for future endeavors.

Identifying the needs and service gaps in pediatric neuro-oncology

The Inaugural St. Jude–VIVA–NCMCS Pediatric Hematology/Oncology Forum, co-hosted by St. Jude Children's Research Hospital, National Children's Medical Center (Shanghai), Shanghai Children's Medical Center and the Viva China Foundation in 2018, convened a workshop dedicated to childhood CNS tumors, which was attended by stakeholders from major children's hospitals and oncology centers across China. In a follow-up survey aimed at understanding the current status and potential hindrances for delivering neuro-oncology care, participating clinicians indicated that delayed treatment, lack of routine multidisciplinary care teams (MDTs), and treatment abandonment are the most frequent challenges negatively affecting patient care in their practices. In parallel, these issues were acknowledged by the National Health Commission of the People's Republic of China (NHC), which in August 2019, announced a national strategy to address the deficiencies for treating children with cancer, including malignant solid tumors.[13] The diverse nature of malignant solid tumors, aggressive disease course, needs for complex medical services, protracted and costly treatment regimens, and burden on families were identified obstacles for treating such tumors. The NHC policy outlined three key objectives for improving patient survival: (i) enhance the clinical infrastructure and level of care, (ii) ensure access to therapeutic agents and comprehensive insurance coverage, and (iii) facilitate implementation with a top-down yet concerted approach. Recognizing the current status of the pediatric neuro-oncology service in China is a major milestone for addressing pediatric oncology service gaps.

Estimating the burden of pediatric CNS tumors through cancer registries

Comprehensive, population-wide registration of newly diagnosed childhood cancer cases remains the gold standard for evaluating disease incidence and trends. Deficiencies in diagnosis and case registration lead to underestimated disease burdens, and adult cancer registries fail to capture precise estimation of pediatric-specific conditions. CNS tumors are known to be underreported in LMICs.[2] Building a national childhood cancer registry in China is an onerous task because of its large and shifting population, requiring a laborious and coordinated effort through provincial and municipal registries to enroll patients from thousands of centers. The central government established the National Central Cancer Registry in 2002 and subsequently launched the National Program of Cancer Registries in 2008, which collects, analyzes, and disseminates cancer data through a growing number of local registries in China.[14] In 2015, a cancer epidemiology report of 368 qualifying registries covering more than 300 million people provided proof of principle that such data for the country becomes increasingly comprehensive and representative.[15] However, the current framework and resultant epidemiology reports lack a pediatric focus. This limits the ability for administrators, health care providers, and researchers to leverage data from available resources on pediatric cancer-related policy-making, and work and service planning.

One of the earliest epidemiologic studies of pediatric cancer in China reported the childhood leukemia incidence in Shanghai in the 1970s.[16] The Shanghai Cancer Registry has since continued to serve Shanghai, leading to the launch of the National Pediatric Leukemia Cancer Registry by Shanghai Children's Medical Center in October 2018.[17,18] The Beijing Cancer Registry began collecting such data in 1976 and transitioned to an online health information system in 2003, covering 12 million residents.[19] Together with data from the Hong Kong Registry (established in 1963), these population-based registries report an adjusted incidence of pediatric CNS tumors ranging from 2.1 to 2.59 per 100 000

inhabitants.[17-20] Although these studies suggest a lower incidence of pediatric CNS tumors than in Western countries, such estimates are consistently higher than that determined from a pooled analysis of 145 Chinese regional registries in 2010, which reported a childhood brain tumor incidence of 1.5 per million.[21] Underdiagnosis and underreporting, especially in rural areas, may have contributed to these differences. Furthermore, capturing meaningful epidemiologic data of patients with CNS tumors is not trivial.[22] Specifically, the complex and evolving taxonomy of CNS tumors, fragmented clinical care, prevalence of histologically benign but clinically devastating tumors, need for meticulous cataloging of sites of involvement, and importance of registering disease progression rather than relapse represent particular challenges for forming a centralized CNS tumor registry. However, this highlights the need and opportunity to complement the National Cancer Registry by refining registration of CNS tumors in children across the country.

Soliciting cross-disciplinary input and establishing referral networks

Multidisciplinary input is key to achieving satisfactory outcomes for children with CNS tumors.[23] Timely recognition by caregivers and referral from primary care centers, informative radiographic imaging and staging, maximal yet safe neurosurgical resection, timely neuropathologic interpretation, standardized regimens of adjuvant therapy with necessary supportive care, and coordinated long-term surveillance are indispensable for successfully treating most pediatric CNS tumors.[10,11,24] Despite advances in medical training and the availability of diagnostic and therapeutic resources within the country, Chinese patients and families frequently encounter difficulties receiving coordinated care from specialized centers. A lack of relevant specialists within initial treatment centers (often a neurosurgical unit), suboptimal communication among disciplines within institutions, unavailability of regional referral pathways, undefined standards of care, and demand for second opinions in China and internationally are all contributing factors for these difficulties. This can be frustrating for patients and families who have just received the bad news of a brain tumor diagnosis, confusing them with mixed opinions and leading to inadvertent delays for starting adjuvant therapy. A study by Liu and colleagues showed that even in the context of a tertiary referral institution in Beijing, 58% of children with MB began receiving adjuvant radiation therapy more than 25 days after resection. This, in turn, reduced survival, as compared with those who received radiation earlier in international clinical trials.[24,25]

These deficiencies necessitate establishing MDTs in the referral centers capable of offering multimodal therapy for children with CNS tumors.[10,23] Primary and secondary care centers should partner with tertiary regional and/or national institutions via a hub-and-spoke model to ensure timely referral and adequate continuity of care.[26-29] In 1997, Chinese health care providers collaborated to establish the Chinese Children's Cancer Group (CCCG), which is a national consortium pioneered by more than 20 tertiary pediatric oncology centers. In conjunction with St. Jude Children's Research Hospital, CCCG raised the survival rate of childhood ALL in China from 30% to over 80% by supporting and standardizing treatment approaches and conducting large-scale randomized clinical trials.[7,8,30] Building on the success of ALL outcomes, the CCCG CNS tumor working group recently published two standard-of-care guidelines for children with MB and intracranial germ cell tumors.[31,32] These diagnostic and management guidelines reinforce the need for coordinated MDTs, adapting accepted risk-stratified protocols and considering potential restrictions at local institutions. Increasing telemedicine usage will enable real-time consultations with reference centers and laboratories to assist interpretation of radiographic and histopathologic findings and thereby formation of appropriate treatment plans.[33-35] In 2017, Beijing Children's Hospital, Shanghai Children's Medical Center, and Children's Hospital of Fudan University were approved by the National Health and Family Planning Commission (renamed to National Health Commission in 2018) as National Center for Children's Health. These designated centers of excellence will serve Chinese children with CNS tumors by offering quality clinical care, fostering national and international collaboration, providing structured training for health professionals and facilitating capacity building in centers across the country.

Abandonment, financing treatment, and loss to follow-up

Treatment abandonment is defined as a failure to start or complete potentially curative therapies.[36-39] This is more frequent in LMICs and contributes to the proportion of patients with treatment failure.[37,39] Twenty years ago, 70% of children with ALL in China did not complete therapy.[40] Financial constraints, travel distances, along with prolonged and complex treatment courses, uncertainties in outcomes, and fear of toxicities were the main reasons underlying such difficult parental decisions. However, the proportion of patients who did not complete treatment decreased to 20% at a single institution and to only 3% in the latest CCCG-led ALL study.[41,42] This improvement is attributed to the enhanced national health insurance program, which finances the cost for pediatric leukemia treatment, and to better informed patient families. Nevertheless, treatment abandonment for children with CNS tumors is not fully acknowledged and should be addressed. A study conducted at Xinhua Hospital, a university-affiliated tertiary center in Shanghai, revealed that 21 of 67 children (31%) with MB treated from 2007 to 2013 abandoned treatment, which was the most substantial predictor for disease progression in their analysis.[43]

A follow-up survey disclosed the most highly ranked motivations for abandoning treatment: (i) postoperative adverse effects and preference for alternative medicine, (ii) belief that CNS tumors are incurable, (iii) confusion regarding diagnosis and treatment, (iv) financial burden, and (v) transportation difficulties. In another report from the same institution on children with atypical teratoid/rhabdoid tumors (ATRT) who were treated between 2010 and 2015, 10 of 22 patients refused adjuvant treatment after surgery and subsequently succumbed to their disease.[44] The underlying reasons for treatment refusal were not documented, but the inferior prognosis for ATRT, in addition to the challenges described earlier, may have affected patient/family decision-making. Despite the anecdotal and institution-based data, the alarming rate of treatment refusal requires urgent attention and appropriate interventions with psychosocial, family and palliative support.[36,42,45,46]

MB is the most common malignant CNS tumor of childhood and a prototypical example for cost consideration because the standard therapy comprises surgery, radiation and chemotherapy. The estimated cost for treating MB in China is US $20 000, almost double that of ALL.[43] Importantly, the nationwide per capita income is US $1098.[47,48] Patients from rural areas with lower socioeconomic status are more likely to refuse treatment due to the financial implications of care.[49] Residents from these areas are further affected by a lack of insurance and variable reimbursement rates (home province versus out-of-province consultations) for those who are covered. Caring for a child with a CNS tumor exacerbates wealth inequality and poverty, limiting options for treatment and subsequent rehabilitation, thereby reducing quality of life. The New Rural Cooperative Medical Scheme, launched in 2003, has enrolled 99% of rural residents as of 2015, complementing the urban basic medical insurance schemes to provide almost universal social health security coverage.[49] Since 2010, full reimbursement has been offered for childhood ALL treatment, and augmented support for other childhood cancers is underway in accordance with the 2019 NHC statement. This policy will most likely relieve the financial hardships associated with pediatric CNS tumor management and allow patients to complete therapy in tertiary pediatric oncology units. Recognizing family reluctance to proceed with adjuvant therapy and addressing underlying questions, needs, and fears with educational materials, psychological counseling, and social support (e.g. housing and transportation for nonlocal patients and parent groups) will further mitigate the risk of treatment abandonment.[39,50-52]

Long-term follow-up data after completion of treatment are also lacking, as evidenced by only one study from mainland China identified among 59 in a recent systematic review of the chronic health effects of pediatric cancer survivors in Asia.[53] The long-term evaluation of children with CNS tumors is critical not only for detection of later relapses but also for surveillance of disease and treatment-related adverse effects, including neurodevelopmental, endocrine, and vascular deficits or secondary malignant neoplasms.[54,55] The actual extent of loss to follow-up for Chinese children with CNS tumor is unknown and warrants systematic evaluation.

Advancing the level of care within China and beyond

Improving care for thousands of Chinese children with CNS tumors per year is not a task that a single hospital or organization can undertake, calling for the leadership by multi-center collaborative groups. Recognizing the currently available infrastructure and the expertise and limitations of administrators, clinicians, researchers, and benefactors in China represents an exceptional opportunity for improving outcomes for children with CNS tumors. Periodic scrutinization of data collected on the expanding nationwide registries will facilitate continued assessment of service gaps in patient care in local settings. The relatively low incidence of pediatric CNS tumors and increasing number of rare or subtype-specific diseases render the feasibility of prospective comparative trials challenging. Pediatric CNS tumor studies by commonly require decade-long recruitment periods and are frequently outpaced by concurrent biologic discoveries, reducing the relevance of the original research questions. Standardizing and centralizing the treatment for children with CNS tumors in China therefore not only benefits patients within the country but also permits researchers to address scientific questions that cannot be answered by existing pediatric oncology consortiums within reasonable time frames.[28] Studies in pediatric oncology over the past decade confirm the increasing contributions from Chinese researchers.[56] To further facilitate the progress of clinical research, the Chinese government published the Technical Guidelines for the Acceptance of Overseas Clinical Trial Data for Drugs in 2018, supporting new drug applications with the National Medical Products Administration based on foreign clinical trial data.[57]

Research specifically relevant to the Asian population, such as the effects of ethnicity on disease incidence, treatment response, and drug metabolism, may be explored.[20,58-60] Studies on intracranial germ cell tumors, a condition which is up to eight times more common in children of Asian ethnicities, could be conducted in Chinese centers in a relatively efficient manner, while generating scientific data that are highly pertinent to the regional population.[61] Ethnic-specific pharmacogenomics in cytotoxic therapy could be addressed and refined dosing regimens instigated.[58,62,63] Traditional Chinese medicine, which is used by more than half of Chinese families as complementary or alternative therapies for children with cancer, may aid the discovery of novel therapeutic

agents.[64] Establishing pediatric neuro-oncology centers within the country can practically benefit other LMICs within Asia, allowing expanded clinical and academic collaborations.

Conclusion

Providing comprehensive, multidisciplinary care for children with CNS tumors in China is an immediate challenge from a global health perspective. The collaborative efforts for tackling these unmet needs present an unprecedented opportunity to advance pediatric neuro-oncology care and improve outcomes within the country and beyond.

CONFLICT OF INTEREST

The authors disclose no conflict of interest.

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How to cite this article: Liu APY, Moreira DC, Sun C, Krull L, Gao Y, Yang B, et al. Challenges and opportunities for managing pediatric central nervous system tumors in China. Pediatr Investig. 2020;4:211-217. https://doi.org/10.1002/ped4.12212