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Treatment of childhood cancer in China: Current status and future direction

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Introduction

China has a population of 1.3 billion and 16.6% of the population (212 million) is below age of 15 years according to the sixth national census in 2010.[1] Chinese National Central Cancer Registry (NCCR) collected data from 219 cancer registries distributed in different parts of China. In 2010 data from NCCR reported that childhood cancer comprised approximately 0.6% of all cancers. In a recent study analyzed data from 145 cancer registries in China, the age-standardized incidence rate of childhood cancer was 87.1 per million. The top five commonest childhood cancers were leukemia (35.6 per million), central nervous system (CNS) tumor (15.0 per million), lymphoma (6.4 per million), bone cancer (4.4 per million) and kidney cancer (3.7 per million).[2] The incidence is lower than western countries but similar to those reported by other low-middle income countries. The reasons for lower incidence of childhood cancer may be related to incomplete data collection. In China, there is a large floating population, 221 million, who were not permanent residents in locations they worked and might not be included in the city registration. The projected number of new cases of childhood cancer in 0–14 years is 22 875, and new cases of leukemia projected to be 8943 in 2015. It is important to have accurate data on incidence and survival that will help the government in policy making on health care delivery.[3]

History of treatment of childhood cancer in China

The development of pediatric oncology as a subspecialty started in late 1970s. Dr. Yamei Hu from Beijing Children's Hospital is the first pediatrician in China to conduct research in childhood leukemia in 1970s.[4] Some hospitals established special teams under department of pediatrics and surgery to take care of children with leukemia and solid tumors. In 1997, the formation of Chinese Children Cancer Group (CCCG) under the China Anti-Cancer Association was a milestone in development of pediatric oncology service. The various specialties participated in the discussion of solving the practical clinical problems, from diagnostics to treatment. Pediatric hematology and other subspecialties including pediatric surgical oncology, radiotherapy, radiology and pathology could have discussion on collaboration under a common platform. The department of pediatric hematology in many hospitals gradually evolved into departments of pediatric hematology/oncology. Pediatric surgery had

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long history of taking care of solid tumors in children, from diagnosis to management including surgery and chemotherapy. Some hospitals developed the multi-disciplinary approach with better delineation of roles in management of childhood cancers. With the collaboration among various specialties in a hospital, a comprehensive cancer treatment plan was established in some hospitals. In the late 1990s, some regional collaboration started in some more developed cities such as Beijing, Shanghai and Guangzhou. Some standard treatment protocols were prepared and introduced to other hospitals in nearby region for adoption. China is a large country and the standard of management of childhood cancer varies quite a lot among different parts of the country. In the more developed regions, the standard is now approaching that of the developed countries.

Challenges in management of childhood cancer in China

Accessibility to cancer care

The type of cancer treatment offered to children in China is quite variable, depending on geographical and economical situation. The children cancer units are located mainly in big cities, either in children hospitals or big general hospitals (usually university teaching hospitals). Traditionally the leukemia and lymphoma were managed by hematologists in department of pediatrics, whereas solid tumors (including surgery and chemotherapy) are managed by pediatric surgeons. There are some specialized hospitals taking care of brain tumors, bone tumors and retinoblastoma. Most of the patients are referred to the large centers for diagnosis and treatment. In the past, some big centers could not cope with the demand of large patient volume and patients had to wait for longer time to receive treatment. With the expansion of health care system, building new hospitals and setting up more children cancer units, patients can now have access to cancer care in nearby hospitals. However, some families still seek specialized care in big cities hoping for better outcome.

Affordability of treatment of childhood cancer

Affordability to expensive medical cost in treatment of childhood cancers was the major barrier for optimal care. In the past, abandonment of treatment was one of the most important hurdle and the reported abandonment rate in early 2000s was up to 50%.[5,6] The central government started the health care insurance program which also covered children with serious illnesses. China's social health insurance schemes including the rural new cooperative medical scheme (NCMS; launched in 2003) and urban resident-based basic medical insurance scheme (URBMI; launched in 2007) had significantly improved the access to medical treatment.[7] The abandonment rate has dropped to less than 10% in recent years.[5]

Hardware supporting treatment of childhood cancer

With the improvement of health insurance system and rapid increase in number of patients demanding for medical care, many centers are now operating at >100% bed occupancy rate and some patients are turned away because hospital beds are not available. There are many new hospitals built or expansion of existing hospitals to cope with the demand in recent years. Training of health care team to manage children cancer is required. New generation of diagnostic equipment are installed to facilitate early and accurate diagnosis, e.g. CT scan, MRI scan and PET scan. Radiotherapy facilities are also upgraded and proton therapy is also newly introduced. Immunophenotyping, molecular diagnosis and genetic tests for leukemia and childhood cancers are now easily available in many large hospitals. There are now some diagnostic technology companies providing new genetic testing at a short turn-around time. Some companies also offer whole genome sequencing for possibility of target therapy in some high risk malignancies.

New treatment and recent advances

Some advanced centers in China introduced new treatment and achieved excellent treatment outcome. Shanghai Children's Medical Center has a large stem cell transplant unit with over 150 transplant performed each year. Nanfang Hospital also performed transplant with novel regimen with excellent outcome.[8] Chimeric antigen receptor T-cell (CART) treatment is recently reported to have good result in refractory leukemia in US. China is now also actively engaged in CART clinical trials and probably the country with largest number of patients recruited into the clinical trials. Beijing Children's Hospital has developed CD19 and GD2 CART for more than 50 patients with relapsed or refractory leukemia and neuroblastoma. Shanghai Children's Medical Center also developed the in-house CART therapy for acute lymphoblastic leukemia (ALL). Surgical treatment of childhood cancer is also at high standard with capacity to handle complex conditions.

Multicenter collaborative studies

There is great variance in treatment standard across the country and it is also impossible to centralize most of the cancer cases in the developed centers. From early 2000s, the improvement of the socio-economic condition hastened the formation of some collaborative groups. There are two national groups initiated collaborative clinical studies. The Chinese Children Leukemia Group (CCLG) started the CCLG-ALL 2008 Study. A total of 2231 patients were recruited from 10 hospitals across the country from 2008 to 2013.[9] Recently CCLG organized another two clinical trials on childhood acute myeloid leukemia (AML) and acute promyelocytic leukemia (APL), namely CCLG-AML 2015 study (2015–2018)

and CCLG-APL 2016 study (2016–2019), respectively. These studies included randomization questions on choices of induction or maintenance chemotherapeutic agents (Table 1).

CCCG under the China Anti-Cancer Association has prepared or under preparation of the following treatment protocols which form the treatment guidelines for all centers in China: neuroblastoma, germ cell tumor, hepatoblastoma, renal tumor, mature B lymphoma and CNS tumors.[10] These guidelines however are not formal research protocols and only serve as treatment recommendation. CCCG has organized one of the largest clinical trials in China, the CCCG-ALL-2015 Study. The Study is led by the National Center for Children's Health (Shanghai) and supported by St Jude Children's Research Hospital and the VIVA Foundation. Up to January 2019, and 6024 patients were recruited into the study. A randomized study comparing two different tyrosine kinase inhibitor (imatinib versus dasatinib) was also completed.[11]

Other than prospective studies, the Group also conducted retrospective studies on some rare conditions.[12]

Other than the two national groups, some hospitals also initiated regional multicenter studies. Shanghai Children's Medical Center started a SCMC 2005 Study with 5 centers participating.[13] In south China, there was a longer history of multicenter studies. In 2002, the Guangzhou Childhood Leukemia Group (GZCLG) started the first pediatric ALL study. Seven hospitals in Guangzhou city joined the study with 446 patients recruited.[14] The GZCLG later expanded to form the Guangdong Province Childhood Leukemia/lymphoma Group (GDCLG) with more hospitals from different cities in the Province joining, the diseases studied also extended to include APL. The GD-2008 ALL study with 9 hospitals participated with over 1700 patients recruited.[15] The Group further expanded to South China Children Cancer Group (SCCCG) in 2016 with 22 hospitals joining. The multicenter clinical trials in SCCCG also include Wilms tumor and non-Hodgkin's

TABLE 1 Multicenter clinical trials in China

Name	Organization or leading institution	Patients recounted	Date started	Date ended	Research questions
CCLG-ALL 2008	Chinese Children Leukemia Group	2231 (10 hospitals)	04/2008	12/2013	RCT on maintenance treatment
CCLG-AML 2015	Chinese Children Leukemia Group	Up to 03/2018 853 (37 hospitals)	07/2015	12/2018	RCT at induction of etoposide vs homoharringtonine; RCT at maintenance of cytarabine vs ATRA
CCLG-APL 2016	Chinese Children Leukemia Group	Up to 03/2018 102 (52 hospitals)	07/2016	12/2019	Testing oral arsenic compound without chemotherapy in standard risk
CCLG-ALL 2015	Chinese Children Cancer Group	Up to 03/2018 4015 (20 hospitals)	11/2014	2019	RCT on maintenance treatment, dasatinib vs imatinib for Ph ALL
GZ-2002 ALL	Guangzhou Childhood Leukemia Group	443 (7 hospitals)	10/2002	06/2009	Single arm for standard risk and intermediate risk
GD-2008 ALL	Guangdong Province Children Leukemia Group	1721 (9 hospitals)	02/2008	03/2016	RCT on maintenance treatment, reference for BFM
SCCCG-2016 ALL	South China Children Cancer Group	on going (17 hospitals)	08/2016	—	Apply MRD for risk stratification; study more intensive Peg-L-ASP in intermediate risk
SCCCG-APL	South China Children Cancer Group	120 (15 hospitals)	09/2011	08/2020	The cooperation of ATO and oral RIF on the treatment of childhood APL
SCCCG-2011 Wilms Tumor	South China Children Cancer Group	Up to 03/2018 132 (12 hospitals)	04/2011	12/2020	RCT of radiotherapy versus no radiotherapy in favorable histology Wilms tumor Stage 3A
SCCCG-NHL-2017 BL/DLBCL	South China Children Cancer Group	Up to 03/2018 50 (22 hospitals)	07/2017	12/2022	Rituximab combined with NHL-BFM-95 protocol for intermediate risk and high risk Chinese pediatric BL/ALL and DLBCL
SCCCG-NHL-2017 ALCL	South China Children Cancer Group	Up to 03/2018 20 (22 hospitals)	07/2017	12/2022	Improvement of risk stratification and treatment for Chinese pediatric systemic ALCL
SCCCG-NHL-2017 LBL	South China Children Cancer Group	Up to 03/2018 25 (22 hospitals)	07/2017	12/2022	Improvement of risk stratification for Chinese pediatric LBL by combining gene and PET/CT evaluation

ALL, acute lymphoblastic leukemia; APL, acute promyelocytic leukemia; AML, acute myeloid leukemia; NHL, non-Hodgkin's lymphoma; BL/DLBCL, Burkitt lymphoma/diffuse large B-cell lymphoma; ALCL, anaplastic large cell lymphoma; LBL, lymphoblastic lymphoma; RCT, randomized controlled trial; ATRA, all-trans-retinoic acid; Ph, Philadelphia chromosome; BFM, Berlin-Frankfurt-Muenster; ATO, arsenic trioxide; RIF, Realgar-Indigo naturalis formula; MRD, minimal residual disease; PET/CT, positron-emission tomography/computed tomography.

lymphoma (NHL). SCCCG-Wilms tumor-2011 and SCCCG-NHL-2017 are ongoing. Some of the completed and ongoing clinical trials are listed in Table 1.

The future development of pediatric oncology research in China requires a more structured organization to oversee the registry, data management, development of clinical trial protocols and proper conduct of multi-center trials. At the moment, the two national organizations do not have a permanent structure to oversee the research activities. There are some ad hoc studies ongoing which are investigator initiated and resources are always limited. Data collection and data quality is one of the most challenging tasks in multicenter studies. The individual institutions do not have dedicated manpower as data managers. Not uncommonly some junior doctors or post-graduate students or nurses are assigned for data management. However, there may not be training for these data specialist and they are also not full time staff for such research purposes. In the past experience, chasing of missing data is very time consuming and sometimes unrewarding. In recent years, some institutions can obtain research funding from university or government research grant, this may help to employ some dedicated staff in data management which will improve the data quality. In the most recent multicenter study with large number of patients recruited, the CCCG 2015 Study already has over 6000 subjects, the data management is particularly important. Fortunately the study could obtain grant support from the non-government organization, VIVA Foundation. The funding support is essential to maintain a central data office, support to individual hospitals to employ staff to handle data, and more important is the conduct of site audits.

Whether the several China groups should merge into one huge national group is not certain. The logistics would be more complicated in view of the huge population and also variations in the study group settings. The experience from North America and Japan may be good reference, it took several decades of building trust among several collaborative groups to merge into one large national group.

CONFLTCT OF INTEREST

None.

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