PEDIATRIC ONCOLOGY

Toward the Cure of Acute Lymphoblastic Leukemia in Children in China

Si-Liang Chen, MD[1]; Hui Zhang, MD, PhD[3]; Robert Peter Gale, MD[4]; Jing-Yan Tang, MD[5]; Ching-Hon Pui, MD[6]; Sai-Juan Chen, MD[2]; and Yang Liang, MD, PhD[1]

abstract

This study explored results of therapy of children with acute lymphoblastic leukemia (ALL) in China, recent progress, and challenges. Included are a survey of therapy outcomes of ALL in Chinese children nationwide, comparison of these data with global ALL therapy outcomes, analyses of obstacles to improving outcomes, and suggestions of how progress can be achieved. Therapy outcomes at many Chinese pediatric cancer centers are approaching those of resource-rich countries. However, nationwide outcomes still need improvement. Obstacles include suboptimal clinical trials participation, children without adequate health care funding, human resource shortages, especially physicians expert in pediatric hematology and oncology, and social-economic disparities. We suggest how these obstacles have been and continue to be remedied including expanded access to protocol-based therapy, improved supportive care, health care reforms, recruitment of trained personnel, and international collaborations. China has made substantial progress treating children with ALL. We envision even better outcomes in the near future.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL), the most common childhood cancer, is now one of the most curable.[1,2] This achievement resulted from better understanding of leukemia biology,[3] identifying new subtypes of ALL with prognostic and therapeutic relevance,[4] new therapy strategies,[5] advances in supportive care,[6] and increased multidisciplinary collaboration.[7,8] In resource-rich countries, 80%-90% of children with ALL are cured. Some survivors have long-term sequelae but most do not.[9]

China began focusing on ALL as a high-priority health issue in the early 2000s. In 2017, China had 233 million children ≤ 14 years of age, accounting for 17% of the population.[10] This proportion is lower than in the United States and European Union countries, probably as a result of China's 33-year-long one-child policy. Several factors have impeded progress in treating Chinese children with ALL, including uneven or insufficient health care coverage and other issues discussed below. We highlight areas of concern and recommend solutions.

EPIDEMIOLOGY AND CURRENT OUTCOME OF CHILDHOOD LEUKAEMIA IN CHINA

Comprehensive epidemiologic data on childhood cancers are available in resource-rich countries.[11] There are no similar data in China because of the sporadic coverage of hospital-based or population-based registries and inadequate diagnostic methods. The China Cancer Registry Annual Report 2017[12] covering 449 sites and 288 million children and adults published annual leukemia incidence rates of 3.19, 5.54, 3.49, and 3.12 per 10E+5 population for ages 0-1, > 1 to < 5, 5 to < 10, and 10-14 years. Comparable US data from the Surveillance and Epidemiology End Results-9 registry 1990-2011 indicate annual leukemia incidences of 7.5, 3.7, 2.6, and 2.6 per 10E+5 for ages 0 to < 5, 5 to < 10, 10 to < 15, and 15-19 years.[13] A direct comparison of incidence rates is impossible because of using different age cut points. The 6th National Census of China provided population information and estimated 10,000 new cases of leukemia annually in children < 15 years of age based on normalized age groups.[14] Realizing the importance of cancer registry to advance research and treatment of children with leukemia, a Chinese National Leukemia Cancer Registry was established in October 2018 under the management of the National Children's Medical Center (Shanghai, China). Figure 1 displays data on incidences and deaths from childhood leukemia. Death rates differ by geospace, partly reflecting incomplete reporting of infant deaths and socioeconomic factors in rural China. The high rate of leukemia not otherwise specified in Figure 1C reflects poor diagnostic accuracy in rural compared with urban geospaces and needs improvement. The high mortality of children

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

One in every five children with acute lymphoblastic leukemia globally is in China. As such, worldwide progress requires bringing China's nationwide therapy outcomes to the same level as resource-rich nations. Therapy outcomes at some Chinese pediatric cancer centers are approaching this goal but the nationwide success rate is lower. We discuss reasons why some of which include inadequate clinical trials participation, under-insured children, human resource shortages, and social-economic disparities.

Knowledge Generated

We suggest how these deficits have been and continue to be remedied including expanded access to protocol-based therapy, improved supportive care, health care reforms, recruitment of trained personnel, and international collaborations.

Relevance

We envision substantial improvement in curing Chinese children with acute lymphoblastic leukemia in the near future.

with leukemia not otherwise specified in rural geospaces contributes to the high mortality compared with urban geospaces for the category *all leukemias* (Fig 1E). Economics prevent rural families from seeking referral to national or regional expert centers. Also, because of economics, more rural children are never treated or stop therapy prematurely.

A recent disability-adjusted life year study indicated a significant impact of childhood cancer in China.[15] ALL is the most common childhood cancer in China, like other countries.[15] This disability-adjusted life year analysis indicates therapy of childhood ALL remains an unmet need in China. Data of incidences of childhood ALL by geospace, sex, and age are needed to optimize diagnosis, therapy, research efforts, and perhaps consider prevention efforts.[16,17]

Age-standardized 5-year survival rates in China for childhood ALL have not changed substantially in recent years, 62% (95% CI, 47 to 77%) in 2000-2004 versus 58% (47 to 69%) in 2010-2014.[18] Importantly, these nationwide survival rates are much lower than in the United States and other Asian countries including Malaysia and Singapore (88% [95% CI, 82 to 95%] at 6 years),[19,20] Japan (89% [86 to 93%] at 5 years),[21] and South Korea (89% [78 to 99%] at 3 years[22]). As we discuss below, the nationwide 5-year survival rate for childhood ALL in China is substantially lower than those reported by major Chinese childhood cancer centers.

Reasons resulting in this poor nationwide outcome are complex. First, resource-stratified and risk-directed clinical protocols are lacking, especially in rural geospaces but there is progress because of nationwide health care reforms.[23] Second, more clinical trials are needed to standardize therapy and improve outcomes. Third, we need special attention to underprivileged children, particularly those from rural geospaces. Fourth, the discordance in numbers of pediatric experts between urban and rural geospaces needs correction. Fifth, infection control and availability of blood products need to be improved. Sixth, tension between medical professionals and families needs resolution. Seventh, pediatric oncologists are overworked, underpaid, and insufficiently supported. Eighth, some sociodemographic and socioeconomic disparities need resolution. Finally, we need a holistic care approach to children with ALL.

Despite these limitations, efforts are being made by local medical groups to overcome these obstacles. For example, a study from Hong Kong (HKALL97) reported 4-year event-free survival (EFS) of 79% in 171 children.[24] Recent reports from large Chinese centers are encouraging.[25-37] The 5-year EFS was 68% (66 to 71%) in the Shanghai SCMC-ALL-2005 study of 1,085 children,[37] 80% (78 to 82%) in the Beijing CCLG-ALL-2008 study of 2,216 evaluable children,[36] and 68% (63 to 73%) in the West China CCLG-2008 study of 424 children[35] (Table 1). In a protocol-based study of 92 children with non–high-risk ALL in Shanghai, 6-year EFS was 75% (66 to 85%).[32] Although these rates are lower than those in resource-rich countries, they indicate substantial recent improvement. The China Ministry of Health has adopted contemporary therapy guidelines to improve therapy of childhood ALL.[38]

Issues of availability and cost of laboratory tests needs to be resolved. Many families cannot afford the cost of laboratory studies needed for optimal risk-directed therapy such as mutation topography analyses and measurable residual disease testing. Those tests are typically sent to independent clinical laboratories which are not regulated in quality or cost as they are in resource-rich countries. Furthermore, costs of laboratory tests are typically not reimbursed by medical insurance. These problems could be addressed by government intervention. Another issue is the need to develop comprehensive clinical research teams including physician, nurses, data managers, and statisticians to design and implement clinical trials whose analyses could improve outcomes.

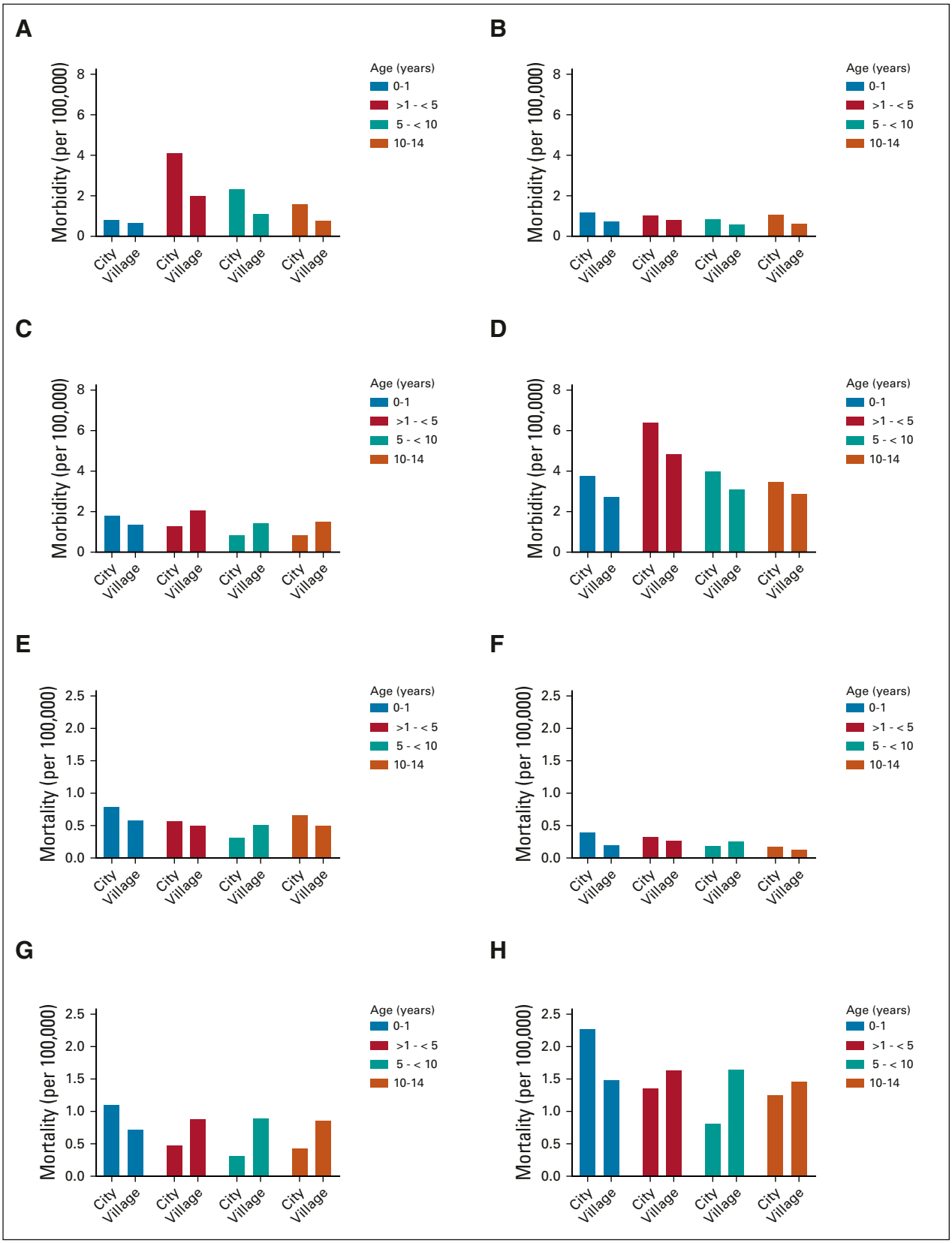

FIG 1. Incidence and death rates of childhood leukemias in China. (A-C) Incidence rates of childhood ALL, AML, and leukemia NOS in different age cohorts; (D) incidence rates of all leukemias in children 0-14 years of age; (E-G) death rates of ALL, AML, and leukemia NOS in different age cohorts; (H) death rates for all types of leukemia combined among children < 14 years of age. AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; NOS, not otherwise specified.

TABLE 1. Recent Childhood ALL Studies in China

References	Study Interval	No. of Subjects	Designation	Risk Stratification	CR Rate, %	EFS, % (95% CI)	Relapse Rate	Median Follow-Up Month (range)	Abandonment Rate, %	TRM, %	Fatal Infections, %
25	2000-2004	58	Rongcheng ALL-98		90	NA	NA	NA	26	NA	NA
26	1998-2002	119	CCLG-97	SR	97	NA	14	46 (20-78)		4	3
27	1996-2006	374	Rongcheng ALL-98		94	5 years, 68 (56 to 80)	11	34 (1-104)	29	7	5
28	1999-2006	169			NA	NA	NA	NA	8	6	4
		46	China-98 protocol			4 years, 80 (69 to 92)					
		73	Modified ALL-IC-BFM2002			4 years, 84 (74 to 94)					
		50	Reduced-intensity			4 years, 73 (59 to 86)					
29	1998-2007	115	ALL-XH-99		90	5 years, 69 (59 to 79)	14	21 (1-84)		14	4
				SR (n = 62)		5 years, 82 (70 to 94)					
				IR (n = 12)		5 years, 77 (48 to 99)					
				HR (n = 41)		5 years, 43 (21 to 65)					
30	1998-2004	248	NPCAC97		97	5 years, 71 (63 to 79)		66 (29-110)	48	9	7
				SR (n = 196)		5 years, 76 (68 to 84)					
				HR (n = 52)		5 years, 51 (35 to 67)					
31	2004-2007	88	2004 protocol		91 (63/69)	4 years, 60 (46 to 74)	18	13	14 (12/88)	9	8
				SR (n = 27)	100	4 years, 76 (56 to 96)	7				
				IR (n = 22)	100	4 years, 66 (42 to 90)	18				
				HR (n = 39)	81	4 years, 44 (20 to 68)	26				
32	2003-2008	92	BFM2002	Non-HR	98	6 years, 75 (65 to 85)	13	72 (53-109)	29 (43/147)	NA	1
			China-98 protocol	Historical control group		6 years, 58 (44 to 72)			51 (61/119)		
33	2005-2009	601	SCMC-ALL-2005	B-ALL	99	5 years, 71 (63 to 79)		38 (1-76)	8 (50)	3	3
				SR (n = 284)		5 years, 83 (73 to 93)					
				IR (n = 231)		5 years, 69 (57 to 81)					
				HR (n = 86)		5 years, 32 (14 to 50)					
34	2010-2013	135	Clinical route 2010	SR	100	3-year OS: 87	11	14 (5-48)		NA	NA
				IR	100	3-year OS: 78	14				
		59	Childhood ALL-2006	SR	100	3-year OS: 89	9				
				IR	100	3-year OS: 85	12				
35	2009-2014	424	CCLG-ALL-2008	424	96	5 years, 68 (62 to 74)	19 ± 3	35 (1-79)	5 (23)	5	4
				SR (n = 152)		5 years, 83 (75 to 91)	10 ± 3				
				IR (n = 170)		5 years, 75 (67 to 83)	15 ± 4				
				HR (n = 102)		5 years, 35 (23 to 47)	46 ± 8				
36	2008-2012	2,231	CCLG-ALL 2008		94	5 years, 80 (78 to 82)	13	47 (0-86)	5 (108)	5	
				SR (n = 868)	98	5 years, 88 (86 to 90)					
				IR (n = 893)	98	5 years, 82 (78 to 86)					
				HR (n = 470)	79	5 years, 60 (54 to 66)					
37	2005-2014	1,085	SCMC-ALL-2005		96	5 years, 68 (66 to 70)		68 (31-124)	4 (42)	1	1
				SR (n = 393)		5 years, 82 (78 to 86)					
				IR (n = 608)		5 years, 67 (63 to 71)					
				HR (n = 84)		5 years, 14 (6 to 22)					

Abbreviations: ALL, acute lymphoblastic leukemia; CR, complete remission; EFS, event-free survival; HR, high risk; IR, intermediate risk; NA, not applicable; SR, standard risk; TRM, treatment related mortality.

PROGRESS IN TREATING CHILDHOOD ALL BY HEALTH CARE REFORM

There remain obstacles to improving the clinical outcomes of Chinese children with ALL. First, the public health insurance system is underdeveloped. Access to and the cost of leukemia treatment in many places in China needs improvement. Second, a robust system is needed to accelerate adoption of new diagnostic and treatment strategies and guarantee reimbursement. Unfortunately, commercial health insurance in China usually cannot be renewed after a cancer diagnosis. Third, the infrastructure required to treat children with ALL needs improvement.[39] Finally, a centralized management system instead of multiple local administrative bodies would increase efficiency of cancer treatment centers.

Since the early 1990s, Shanghai—one of the most economically developed cities in China—has successfully implemented a citywide health insurance program focused on supporting children with catastrophic illnesses including ALL and could be replicated in other urban areas. Nationwide, health care financing system has shifted from government-funded to a multiple partner participation model. However, one potentially undesirable consequence of this progress could be a profit-driven increase in medical costs of diagnostic procedures and prescription drugs leading to medical impoverishment, particularly for rural villagers accounting for 40% (World Bank[40]) of a total 1,397 million Chinese people (World Bank[41]). Finally, the lack of pediatric hematology and oncology subspecialty in many hospitals makes it difficult to provide optimal ALL care. Except for urban medical centers, children with ALL are treated in general pediatric department of comprehensive medical centers, adult hematology department at provincial-level hospitals, or internal medicine department at county or municipality hospitals.

One of the most encouraging developments is the New Rural Cooperative Major Diseases Protection System—a medical care system begun in 2009 to provide coverage to low-income village residents unqualified for urban insurance plans. It is organized by the government and focuses on encouraging farmers to participate. Funding comes from multiple resources including individuals, communities, and the government to construct a support system for catastrophic childhood diseases. The system has increased reimbursement rates of childhood leukemia from 49% to 81%.[42] Data from China Ministry of Health[43] indicate improvements in participation rate (99%), funds (329B RMB; $47B US dollars [USD]), per capita fund (490 RMB; $70 USD), and expenditure of national new rural cooperative medical system fund (299B RMB; $43B USD) in 2015 (Figs 2A-2E). Villagers account for most of the Chinese population considered to be the vulnerable group reflecting low socioeconomic state, education level, and limited health care coverage. The low disposable income in certain regions such as middle and west China poses considerable challenges to families facing a diagnosis of childhood ALL (Fig 2F) with an estimated 100K RMB ($14K USD) needed to meet the total cost of treatment.

Expanding universal insurance coverage for childhood ALL in China can accelerate progress in addressing the deficiencies we discuss. Recent improvements in treating childhood ALL are based on increased understanding of disease biology, risk-directed therapy, and new therapies such as bispecific monoclonal antibodies and chimeric antigen receptor T cells. Development of these therapies is advancing in China but approvals are behind the United States. Interactions between health care authorities, physicians, payors, and families can accelerate progress.

CHILDHOOD LEUKAEMIA CLINICAL TRIALS IN CHINA

Progress achieved in treating childhood ALL underscores the importance of consistent testing of potentially effective therapy options. Data in the Chinese Clinical Trial Registry[44] indicate only 54 childhood leukemia trials out of 398 leukemia trials and 37,376 registered clinical trials. Of the 533 trials in childhood ALL registered inClinicalTrials.gov,[45] only 13 are China-based ClinicalTrials.gov.[46] Based on the population, China should be conducting 20% of the clinical trials in childhood leukemia but its percentage is 10-fold lower. Most of the trials were performed at a few major medical centers in East China (Fig 3). Increased numbers of clinical trials would provide a solid foundation for the improved treatment and clinical research of childhood cancers in China. In the United States, about 60% of children with cancer are treated within a clinical trial.[47,48] In contrast, data from the China drug trials registration website[49] indicate a substantially lower clinical trials enrollment rate. A recent study reported that parents with low health literacy are less likely compared with health-literate parents to enroll their child in a clinical trial.[50] This needs to be addressed by increasing health literacy, especially in rural geospaces.

One encouraging achievement is a partnership between St. Jude Children's Research Hospital and Shanghai Children's Medical Center, which resulted in development of the China Children Cancer Group study. This study included 20 major pediatric cancer centers covering 65% of China's population. From 2015 to 2019, 7,677 children with ALL enrolled in this study.[51,52] The hope is to help an estimated 10,000 children with ALL annually with a clinical trial enrollment rate of 15%.

CHALLENGES TO IMPROVING OUTCOMES IN CHILDHOOD ALL: NEEDS OF LEFT-BEHIND AND LEAST-PRIVILEGED CHILDREN

The pace of development in China has been uneven, ranging from the highly industrialized East to the poorly developed West. This has led to large-scale relocation of rural families to eastern cities and consequently to left-behind children living with their grandparents in villages or with their migrant parents in cities without access to high-quality health care, education, and protection services. These almost invisible groups account for an estimated 40% of Chinese children.[53]

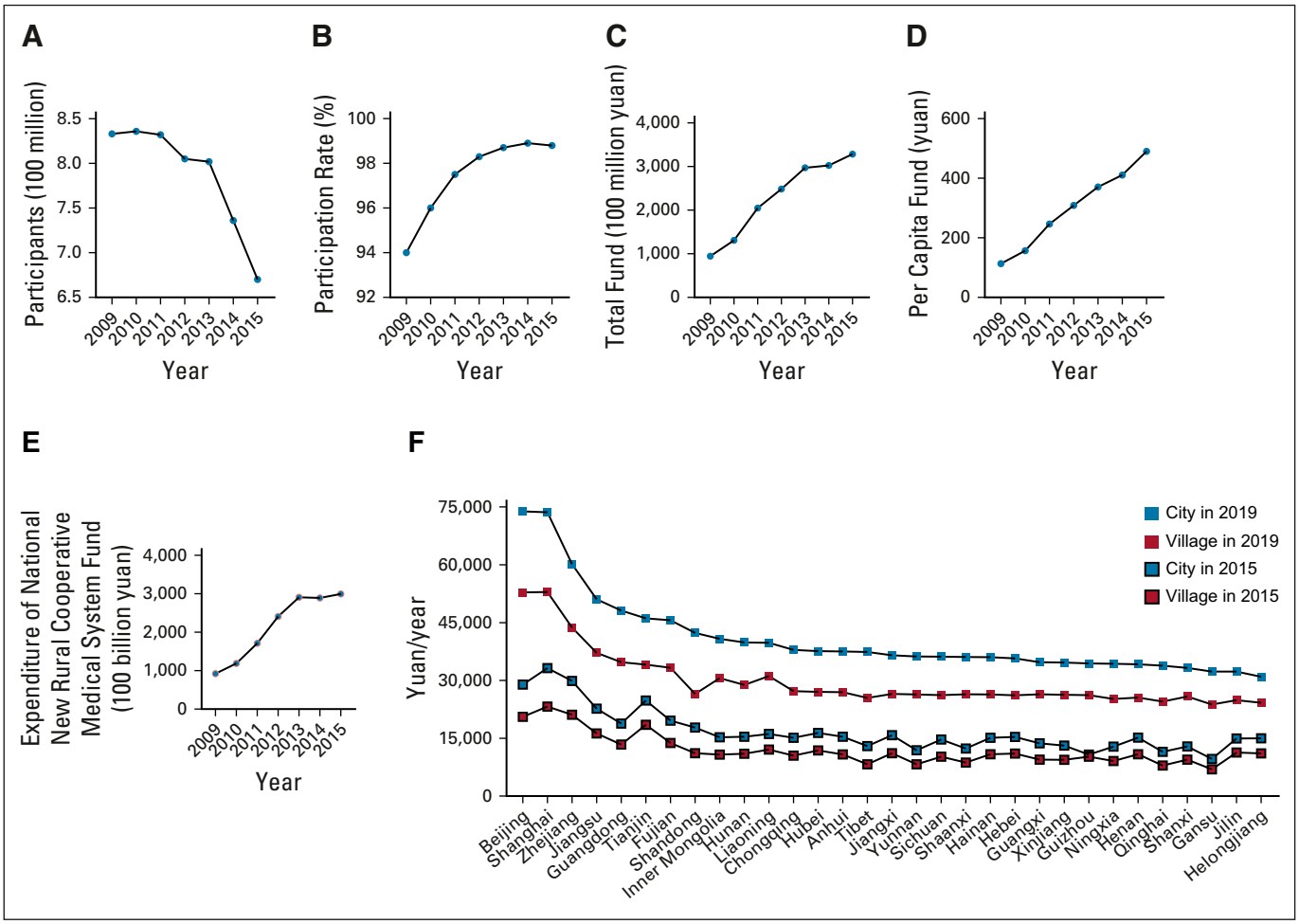

FIG 2. Dynamic change of main parameter of national new rural cooperative medical system and related disposable income. (A) Numbers of subjects; (B) participation rate; (C) total funds; (D) per capita funds; (E) expenditure of national new rural cooperative medical system funds; (F) per capita disposable income in 31 Chinese provinces 2015 and 2019.

The geographic and economic inequalities in China require funding resources to supplement the universal governmental insurance system. The Children's Catastrophic Disease Alliance of China, initiated by the Red Cross Foundation of China, was launched in 2015. In 2016, there was about 3B RMB ($41M USD) allocated to 13,000 children, an average of 22K RMB ($3,200 USD) per child. In 2005, the China Red Cross Foundation established the Little Angel Fund, which helped more than 14,000 and 25,000 children with leukemia from 2005 to 2015 and 2016 to 2020, respectively, and is the largest private leukemia assistance program in China.[54] A survey by the China Youth University for Political Sciences of 1,229 families with children with leukemia reported leukemia treatment costs of < 100K RMB ($14K USD) in 17%, 100-300K RMB ($14-43K USD) in 61%, and > 300K RMB ($43K USD) in 12% of such families.[55] Online fundraising (crowd-sourcing)[56] is another way to raise funding for leukemia research and therapy. However, there are major differences in citizens' perception of whether private parties should contribute to scientific research and medical care among countries. For example, success of crowd-sourcing for medical care in the United States is about four-fold greater than that in the United Kingdom despite similar *per capita* GDPs, whereas similar efforts in Russia are mostly unsuccessful (RPG; personal communication). This likely reflects different health care systems, predominately private in the United States versus governmental in the United Kingdom and Russia. Also, there are tax incentives to charity giving in the United States but not in many other countries. Differences in culture, religion, social awareness, and humanistic values are also important. Crowd-sourcing in China is in its infancy and unlikely to be of great help in improving therapy of children with ALL in the short term.

INFECTION CONTROL, BLOOD PRODUCTS, AND PROTOCOL-BASED THERAPY

In many nonurban settings in China, physicians do not follow contemporary therapy guidelines. Effective education strategies are needed including training more pediatric

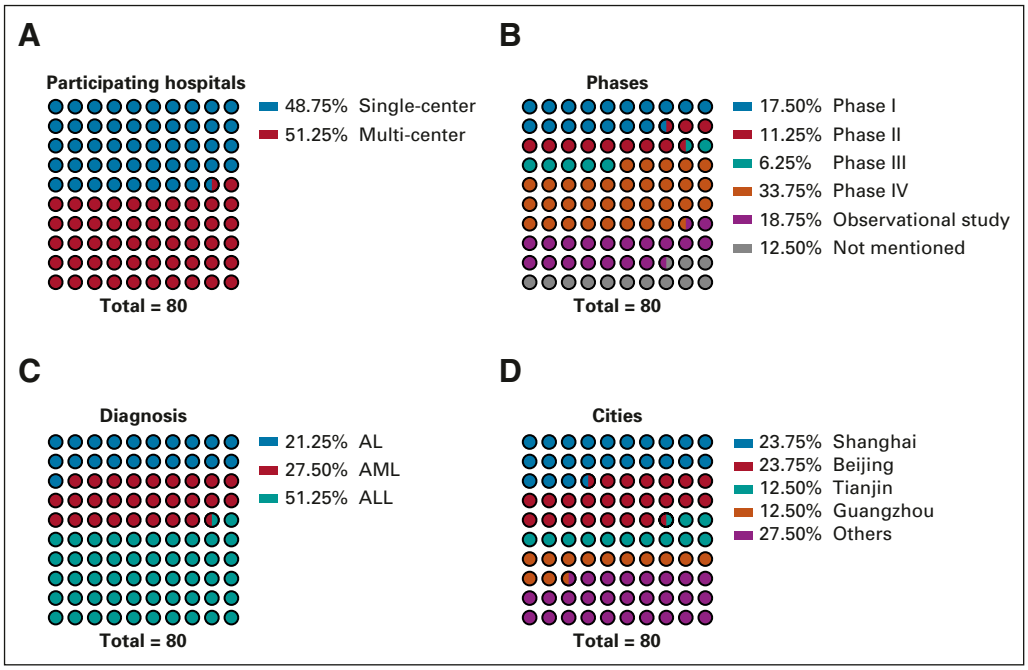

FIG 3. Distribution of childhood leukemia clinical trials in China. A summary of childhood leukaemia-related clinical trials by: (A) single versus > 1 participating center; (B) phase; (C) disease; and (D) region. AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

oncologists. Most well-trained Chinese pediatric oncologists gravitate to urban centers as in most developed and developing countries, resulting in a deficiency of experts in rural areas. Other important factors hindering optimal therapy of childhood ALL include suboptimal infection control and a shortage of blood products.[57] The low cure rates in some local hospitals can be partly attributed to a focus on anti-leukemia therapy without adequate attention to infection control and other supportive care. Greater awareness of effective infection control practices is needed among medical professionals coupled with improvements in hospital facilities led by specialized physicians and nurses. A recent Chinese study emphasized direct economic loss and prolonged hospitalizations resulting from nosocomial infections in children with ALL.[58] Average cost of about 28K RMB ($4K USD) per hospitalization expenses and median hospital stay length of 25 days per patient with an infection versus about 12K RMB ($1.7K USD) per hospitalization expenses and median hospital stay length of 15 days per patient without an infection was reported in this study.

How to improve? First, better hygiene education for medical professionals, nurses, and families. Second, better infrastructure such as more single-bed rooms. Third, strengthen hygiene Standard Operating Procedures. Fourth, a structured antibiotics management scheme. Fifth, better hospital-acquired infection reporting and analyses. Finally, multidisciplinary cooperation to reduce infection deaths.

There has been a nationwide severe blood shortage in China recently because of misconceptions about the safety of blood donation. Local health authorities and blood banks are making efforts to improve this situation. One study reported numbers of volunteer blood donations in Guangdong province, among the most developed provinces, increased 38% from 2006 to 2014, whereas blood donations from relatives decreased by one-half and platelet donations by two-thirds.[59] Efforts to increase blood donations are underway, and better donor education is greatly needed. Eliminating paid blood donation is important to control infection risk to donors and recipients in view of prior outbreaks of hepatitis-B and hepatitis-C viruses and HIV in Chinese paid blood and plasma donors.[60] Concerns over transfusion safety are mostly the result of poor communication between blood bank staff, physicians, and potential transfusion recipients.

DOCTOR-PATIENT-FAMILY DYNAMICS

An unavoidable topic in this discussion is tension in the doctor-patient-family relationship. Most Chinese families have only one child. Consequently, when a child develops ALL, the family exerts tremendous pressure on physicians. Without adequate psychologic and social support, parental stress or unreasonable expectation is often projected onto the health care providers. Sometimes, this has resulted in physical attacks on doctors and nurses. Some doctors are reluctant to use intensive therapies because they fear lawsuits or physical harm. Previous studies reported *defensive* medicine as a major cause of escalating health care costs worldwide.[61,62]

Cai et al[63] reported a nation-level study of workplace violence against health care workers in China from 2013 to 2016. They identified 459 criminal cases involving

patient-initiated workplace violence against health care workers. There was geospatial heterogeneity with lower incidence in less resource-rich western provinces. Primary hospitals experienced the highest rates of serious workplace violence, and emergency departments and doctors were at higher risk compared with other departments and health workers. Perpetrators were primarily male farmers 18-44 years of age with low education levels. The most frequent reason of serious patient-initiated workplace violence included perceived medical malpractice after a patient's death, failed compensation negotiations, and dissatisfaction with treatment outcomes. The murder of Dr Yang in 2020 (Global Times[64]) shocked China and resulted in a new law to protect medical workers' safety. Recently, the *LANCET* published an editorial titled as Protecting Chinese Doctors in support.[65]

PHYSICIAN MANPOWER SHORTAGE

A nationwide survey that covered more than 54,000 hospitals on pediatric resources in China reported a severe shortage of pediatricians.[66] Because of the worsening medical practice environment in China, only about 300 of every 22,000 medical graduates train in pediatrics. Only about 5,000 pediatricians have been trained in China over the past 15 years. In the past 3 years 14,310 (11%) of the registered pediatricians resigned their positions in public hospitals in China. Presently, only approximately 128,000 pediatricians serve 233 million children (1: 1,800) ages 0-14 years. This compares with a pediatrician : child ratio of 1: 800 in the United States, > 2-fold greater than that in China. The mass resignation of Chinese pediatricians resulted from heavy clinical workloads, low income, and tensions with families. The outlook for pediatric oncology in China is dire, considering the recent decision to revise the country's second-child policy.

Chinese health care authorities implemented policies to alleviate the shortage of pediatricians or pediatric nurses including (1) encouraging pediatrics training in medical schools; (2) increasing medical school enrollment of students interested in pediatrics; (3) increasing the income of pediatricians and pediatric nurses; (4) encouraging physician to switch to pediatrics; and (5) encouraging private hospitals to include children's facilities.

SOCIAL ISSUES AND CONTRIBUTIONS OF NONPROFIT ORGANIZATIONS

Broadly speaking, Chinese society lacks an accurate perception of childhood leukemia. Although financial hardship is the most common reason for inadequate therapy, social discrimination is another factor affecting treatment decisions.[67] Families may feel ashamed of their child having leukemia and may become isolated and shamed by others. These factors may contribute to poor compliance during treatment and follow-up. Other factors include a belief leukemia is incurable and fear of immediate and long-term adverse events. In Chinese traditional culture, boys are favored over girls because they promulgate the family name and receive a larger share of household resources. This patriarchal ideology and adoption of prenatal sex identification technology has resulted in a marked sex ratio imbalance. The 6th Census of China reported the sex ratios between males and females 0-14 years of age for cities, towns, and villages are 116, 120, and 118, respectively.[68] However, the male predominance in villages may be considerably higher because not all newborn girls were officially registered. Although pathomiosis affects all children, greater discrimination against females remains a problem in China. China's government has made great strides to reduce sex bias by prohibiting prenatal sex determinations but discrepancies in care remain for females in whom entering therapy and premature termination is more common compared with males.[52]

Given these cultural concerns, the psychosocial support needs for children and families are even greater. Studies in Western countries report that with appropriate psychosocial support, most childhood ALL survivors live long, productive lives and are well integrated into society. Thus, improved psychosocial support may encourage survivors and families battling childhood leukemia.

HOLISTIC CARE

Holistic care in the Chinese medical system is in its infancy. Volunteers from charities and community-based organizations are pioneering efforts to help children with leukemia financially, emotionally, and spiritually. This new phase in the development of the Chinese cancer care system would benefit from a comprehensive care package (eg, psychologic counseling, ward school, religious support, and palliative care) for affected families. Improved psychosocial support throughout therapy and follow-up could be expected to encourage childhood survivors and their families.

Much of the credit for integrating humanistic care into the treatment of cancer in China must go to local charities. Volunteers have assisted governmental policy makers in raising social awareness and have helped children and families through a multidimensional approach including charitable organizations, which rely on government funding and policies for their support. These charities engage in collaborative ventures with other organizations to optimize the allocation of resources and with Internet public welfare platforms to take advantage of their high flexibility, low costs, and capacity for rapid fundraising. VIVA China Children's Cancer Foundation supported the data management of the ALL clinical trials and training and education of physicians and nurses of the Chinese Children's Cancer Group.

Currently, there are different models of holistic care: (1) government and charitable organizations including government funds to support charitable organizations; (2) government policies to support charities with mutual investment; (3) collaborations among charities to optimize

allocation of resources; (4) charitable organizations and Internet public welfare platforms to take advantage of the high flexibility, low cost, large accumulation, and rapid fundraising of the Internet platform; and (5) charities and major medical centers.

CONCLUSIONS AND FUTURE DIRECTIONS

Better health care insurance, more governmental investment at many levels, improved access to childhood leukemia experts in rural areas, increased pediatric hematology and oncology specialists, improved infrastructure, and better supportive care are needed to improve cure rates of Chinese children with ALL. Collaboration between Chinese and overseas colleagues focused on ALL therapy is also important. For example, St Jude Children's Research Hospital's Global Program have been collaborating with the Chinese Children's Cancer Group to conduct National ALL clinical trials to address challenging questions that affect childhood ALL cure rates not only in China but worldwide. Chinese pediatric hematologists and oncologists need access to cytogenetics, next-generation sequencing, and measurable residual disease testing to make appropriate and effective therapy decisions. Pharmacogenetic research would also be important to deciphering the impact of host genetic polymorphisms on the drug metabolism affecting the therapeutic efficacy and adverse events.

Medical reforms providing the most immediate and substantial benefit to Chinese children with cancer require a balanced approach. Reforms should include expanded access to resource-adjusted protocol-based treatments, increased cooperation between childhood cancer centers of excellence and regional hospitals, increased access to laboratory techniques needed for risk-directed therapy, enhanced translational research, better infection control, and appropriate psychosocial support. More pediatric hematologists and oncologists are needed, especially in rural areas. Practices pioneered in resource-rich countries can be applied to tackle these issues in China including expanding pediatric oncology units, fundraising, and organizing family support groups.

Implementation of a tax-exempt law in China, such as the 501(c) (3) status in the United States that grants charitable organizations exemption from taxes, may help raise monies for research and treatment. The Charity Law of the People's Republic of China[69] launched in March 2016 provides a substantial official foundation (eg, Chapter 9; item 80, 82, and 83) to encourage personal, entrepreneur, charity organization, and even international donations through tax-exemption policy.

China's health care system has made remarkable progress since 1949, eliminating many infectious diseases and improving nutrition. However, China now faces more challenging problems it shares with resource-rich countries including cardiovascular disease, chronic respiratory diseases, cancer, diabetes, and obesity. A recent series of publications[70–73] highlight achieving health equity should be China's foremost health goal. The current challenges include incomplete health insurance coverage, uneven health care access, mixed health care quality, escalating costs, and high risk of unsustainable expenditures on health care. In response, the Chinese government has announced the Healthy China 2030 reform initiative to develop an equitable health care system. Meeting these goals will require major reforms in heath financing and health workforce development and a new focus on the health problems of vulnerable populations including women, children, the elderly, the disabled, and low-income populations.

AFFILIATIONS

[1]Department of Hematologic Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China
[2]Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine at Shanghai, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China
[3]Department of Hematology and Oncology, Guangzhou Women and Children's Medical Center, Guangzhou, Guangdong, China
[4]Department of Immunology and Inflammation, Haematology Research Centre, Imperial College London, London, United Kingdom
[5]Key Laboratory of Pediatric Hematology and Oncology Ministry of Health, Department of Hematology and Oncology, Shanghai Children's Medical Center, National Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[6]Departments of Oncology, Global Pediatric Medicine, and Pathology, St Jude Children's Research Hospital, Memphis, TN

CORRESPONDING AUTHOR

Yang Liang, MD, PhD, Department of Hematologic Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, 651 Dongfeng East Road, Guangzhou, 510060, China; email: liangyang@sysucc.org.cn.

EQUAL CONTRIBUTION

S.-L.C. and H.Z. contributed equally to this work. Y.L. and S-J. C. contributed equally to this work as co-corresponding authors.

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AUTHOR CONTRIBUTIONS

Conception and design: Si-Liang Chen, Robert Peter Gale, Ching-Hon Pui, Sai-Juan Chen, Yang Liang
Provision of study materials or patients: Si-Liang Chen, Jing-Yan Tang

Collection and assembly of data: Si-Liang Chen, Robert Peter Gale, Jing-Yan Tang, Yang Liang
Data analysis and interpretation: Si-Liang Chen, Hui Zhang, Robert Peter Gale, Ching-Hon Pui, Sai-Juan Chen, Yang Liang
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Robert Peter Gale

Consulting or Advisory Role: BeiGene Ltd, Fusion Pharma LLC, LaJolla NanoMedical Inc, Mingsight Parmaceuticals Inc, CStone Pharmaceuticals, NexImmune Inc, Prolacta Bioscience, Antegene Biotech LLC, Medical Director, FFF Enterprises Inc, AZAC Inc (partner), Russian Foundation for Cancer Research Support (board of directors), and StemRad Ltd (scientific advisory board)

Ching-Hon Pui

Leadership: Adaptive Biotechnologies
Honoraria: Amgen, Servier, ERYTECH Pharma
Consulting or Advisory Role: Adaptive Biotechnologies
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