Treatment abandonment in childhood acute lymphoblastic leukaemia in China: a retrospective cohort study of the Chinese Children's Cancer Group

Jiaoyang Cai,[1] Jie Yu,[2] Xiaofan Zhu,[3] Shaoyan Hu,[4] Yiping Zhu,[5] Hua Jiang,[6] Chunfu Li,[7] Yongjun Fang,[8] Changda Liang,[9] Xiuli Ju,[10] Xin Tian,[11] Xiaowen Zhai,[12] Jinjin Hao,[13] Qun Hu,[14] Ningling Wang,[15] Hui Jiang,[16] Lirong Sun,[17] Chi Kong Li,[18] Kaili Pan,[19] Minghua Yang,[20] Shuhong Shen,[1] Cheng Cheng,[21] Raul C Ribeiro,[22] Ching-Hon Pui,[22] Jingyan Tang,[1] Chinese Children's Cancer Group childhood acute lymphoblastic leukaemia (ALL) 2015 study group (CCCG-ALL-2015)

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/archdischild-2018-316181).

For numbered affiliations see end of article.

Correspondence to
Dr Ching-Hon Pui, Department of Oncology, St Jude Children's Research Hospital, Memphis, Tennessee, USA; Ching-Hon.Pui@STJUDE.ORG and Dr Jingyan Tang, Department of Hematology/Oncology, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Key Lab of Pediatric Hematology and Oncology of China Ministry of Health, Shanghai 200127, China; tangjingyan@scmc.com.cn

C-HP and JT contributed equally.

Received 13 September 2018
Revised 12 December 2018
Accepted 13 December 2018
Published Online First
31 January 2019

ABSTRACT

Objectives Before 2003, most children with acute lymphoblastic leukaemia (ALL) abandoned treatment, with only approximately 30% treated in China. With the development of national insurance for underprivileged patients, we assessed the current frequency and causes of treatment abandonment among patients with ALL who were enrolled in the Chinese Children's Cancer Group ALL protocol between 2015 and 2016.

Methods Demographic, clinical and laboratory data on patients who abandoned treatment, as well as economic and sociocultural data of their families were collected and analysed. General health-related statistics were retrieved from publicly accessible databanks maintained by the Chinese government.

Results At a median follow-up of 119 weeks, 83 (3.1%, 95% CI 2.5% to 3.8%) of the 2641 patients abandoned treatment. Factors independently associated with abandonment included standard/high-risk ALL (OR 2.62, 95% CI 1.43 to 4.77), presence of minimal residual disease at the end of remission induction (OR 3.57, 95% CI 1.90 to 6.74) and low-income economic region (OR 3.7, 95% CI 1.89 to 7.05). According to the family members, economic constraints (50.6%, p=0.0001) were the main reason for treatment abandonment, followed by the belief of incurability, severe side effects and concern over late complications.

Conclusions The rate of ALL treatment abandonment has been greatly reduced in China. Standard/high-risk ALL, residence in a low-income region and economic difficulties were associated with treatment abandonment.

Clinical trial registration number ChiCTR-IPR-14005706, pre-results.

What is already known on this topic?

- Treatment abandonment was a common problem in the treatment of childhood acute lymphoblastic leukaemia (ALL) in China for many years.
- In 2010, Chinese government expanded its spending on healthcare and developed a new health insurance programme to support the treatment of underprivileged children with ALL.
- With increased access to therapy, a Chinese Children's Study Group was developed to provide protocol-based treatment to a large cohort of patients.

What this study adds?

- The results of this study demonstrate that intensive treatment in standard and high-risk arms of the protocol for patients with unfavourable presenting features or a poor response to remission induction therapy, residence in a low-income region and economic difficulties within the family were all closely associated with treatment abandonment.
- Other factors contributing to this outcome were the perception of incurability, severe side effects of therapy and concern over long-term complications.

INTRODUCTION

Acute lymphoblastic leukaemia (ALL), the most common malignant disease affecting children, accounts for 25% of all childhood cancers. The 5-year event-free and overall survival rates of patients with paediatric ALL have reached 85% and 90%, respectively, in high-income countries.[1] However, these remarkable therapeutic gains have not been translated to patients residing in low/middle-income countries (LMIC).[2] The higher paediatric cancer survival rates in high-income countries compared with LMICs can be partly explained by the degree of government spending on health.[2 3] In countries with inefficient health systems, delayed diagnosis, lack of physicians and nurses, inadequate supportive care infrastructure, limited access to effective treatment, high rates of treatment-related mortality, increased relapse and treatment abandonment are common reasons for poor survival rates.[2–5]

Treatment abandonment, defined as the failure to start or complete a programme of potentially

To cite: Cai J, Yu J, Zhu X, *et al*. *Arch Dis Child* 2019;**104**:522–529.

curative therapy, is a frequent but preventable cause of treatment failure among children with ALL living in LMICs.[6] In some studies in LMICs, patients who abandoned therapy were often excluded from data analyses; hence, any estimate of the impact of treatment abandonment on overall outcome may not be reliable.[7] Although economic difficulties are usually associated with an increased rate of abandonment in LMICs, sociocultural factors and inefficient medical care systems may also exert a critical influence on adherence to treatment.[8–10] Moreover, the causes of abandonment may vary according to specific country and often within the same country as it undergoes economic and demographic transitions. Although studies to identify causative factors and implement preventive measures for treatment abandonment have the potential to advance cure rates of ALL in LMICs, they have not yet been conducted in China. Before 2003, most patients abandoned treatment due to financial reasons and it was estimated that only 30% of children with ALL received treatment in China.[11] Since 2003, this country has experienced a profound economic and demographic transition and the government has progressively expanded its investment in health. In 2010, the New Rural Cooperative Medical Scheme (NRCMS) began to cover most of the treatment expenses of childhood ALL,[12] while paediatric oncology units with trained physicians and nurses, hospital infrastructures and uniform ALL treatment guidelines have been greatly expanded. In the study reported here, we have sought to determine the current rate of and factors associated with treatment abandonment in a large cohort of patients with newly diagnosed ALL who were prospectively enrolled in the Chinese Children's Cancer Group ALL 2015 (CCCG-ALL-2015) study.

METHODS

Patients and methods

This analysis included 20 major hospitals/medical centres in 10 provinces, three central government direct-controlled municipalities and Hong Kong. The catchment areas of these centres contain approximately 65% of the population of China. Enrolment of patients 0–18.9 years of age with a confirmed diagnosis of ALL began on 1 January 2015. Treatment was based on minimal residual disease (MRD)-directed, risk-stratified treatment protocol, modified from St Jude Children's Research Hospital Total XV Study[13] and Shanghai Children's Medical Center (SCMC) ALL 2005.[14]

Treatment

All patients received upfront window therapy with dexamethasone for 4 days, followed by remission induction with prednisone, vincristine, daunorubicin and PEG-asparaginase from day 5 to day 28, and cyclophosphamide, cytarabine and mercaptopurine from day 29 to day 35. Treatment response was evaluated at day 19 and day 46 by morphologic criteria and flow cytometric MRD measurements. Consolidation treatment consisted of high-dose methotrexate every other week for four courses. From week 16 to week 35 of continuation therapy, patients with low-risk disease received daily mercaptopurine and weekly methotrexate with pulses of dexamethasone and vincristine, interrupted by two reinduction treatments consisting of PEG-asparaginase, vincristine, dexamethasone and daunorubicin between weeks 22 and 24 and weeks 32 and 34. Patients with standard or high-risk disease received PEG-asparaginase every 3 weeks and daily mercaptopurine with pulses of doxorubicin, vincristine and dexamethasone after consolidation treatment, interrupted by reinduction treatment consisting of PEG-asparaginase, vincristine, dexamethasone and high-dose cytarabine between weeks 32 and 34. Patients were randomly assigned to receive different durations of pulse therapy with dexamethasone and vincristine during maintenance therapy (online supplementary figure S1). In group A, patients received mercaptopurine and methotrexate with dexamethasone and vincristine pulses every 4 weeks for 64 weeks followed by no pulse treatment until the end of therapy (week 125). In group B, patients received mercaptopurine and methotrexate with dexamethasone and vincristine pulses for 16 weeks followed by no pulse treatment until the end of therapy (week 125).

Study design

The conduct of the protocol included a central review of MRD testing and periodic internal and on-site monitoring and external auditing to ensure protocol compliance and appropriate data management. In this study, we adopted the definition of treatment abandonment proposed by Arora and colleagues,[15] that is, treatment was initiated but not completed. The patients' primary haematologists collected both clinical and demographic data on patients who abandoned treatment between 1 January 2015 and

Table 1 Univariate analysis of demographic and clinical features at diagnosis associated with treatment abandonment

Univariate analysis

Feature	Category	Patients not abandoning treatment n (%)	Patients abandoning treatment n (%)	P value
Age (years)	<1	34 (1.3)	3 (3.6)	0.0151
	1–9	2233 (87.3)	64 (77.1)	
	≥10	291 (11.4)	16 (19.3)	
Sex	Male	1512 (59.1)	46 (55.4)	0.4989
	Female	1046 (40.9)	37 (44.6)	
Leucocyte count ($\times 10^9$/L)	<50	2042 (79.8)	59 (71.1)	0.0707
	≥50	516 (20.2)	24 (28.9)	
CNS status	CNS-1	2401 (93.9)	76 (91.6)	0.0681
	CNS-2	32 (1.3)	0	
	CNS-3	10 (0.4)	2 (2.4)	
	Traumatic without blasts	105 (4.1)	4 (4.8)	
	Intracranial mass	10 (0.4)	1 (1.2)	
Lineage	B	2329 (91.0)	70 (84.3)	0.0502
	T	229 (9.0)	13 (15.7)	
Risk group*	Low	1697 (66.3)	39 (47.0)	0.0004
	Standard/high	861 (33.7)	44 (53.0)	
CR status	CR	2515 (98.3)	65 (78.3)	<0.0001
	No CR	43 (1.7)	18 (21.7)†	
MRD, day 19	Negative	1155 (47.3)	24 (32.4)	0.0127
	Positive	1289 (52.7)	50 (67.6)	
MRD, day 46	Negative	2005 (84.7)	35 (60.3)	<0.0001
	Positive	362 (15.3)	23 (39.7)	
Molecular abnormalities	T lineage	229 (9.0)	13 (15.7)	0.0001
	BCR-ABL1 fusion	101 (3.9)	7 (8.4)	
	TEL-AML1 fusion	496 (19.4)	9 (10.8)	
	E2A-PBX1 fusion	103 (4.0)	3 (3.6)	
	MLL rearrangement	58 (2.3)	7 (8.4)	
	PDGFRB rearrangement	11 (0.4)	1 (1.2)	
	B lineage, other	1557 (60.9)	42 (50.6)	
	Not done	3 (0.1)	1 (1.2)	
Region‡	High income	1445 (56.5)	34 (41.0)	<0.0001
	Middle income	827 (32.3)	26 (31.3)	
	Low income	286 (11.2)	23 (27.7)	

*Initial risk determined at diagnosis.
†Eighteen patients abandoned treatment before end of induction; they were deemed 'no CR.'
‡High-income region, upper third of the average per capita disposable income (PCDI) in 2016; middle-income region, middle third of the average PCDI; low-income region, lower third of the average PCDI.
CNS, central nervous system; CR, complete remission; MRD, minimal residual disease.

Table 2 Multivariate analysis of demographic and clinical characteristics associated with treatment abandonment

Feature	Category	Patients not abandoning treatment n (%)	Patients abandoning treatment n (%)	OR (95% CI)	P value
Age (years)	1–9	2058 (97.9)	44 (2.1)		
	≥10	267 (95.4)	13 (4.6)	1.07 (0.51 to 2.16)	0.8539
	<1	24 (96)	1 (4.0)	1.06 (0.06 to 5.85)	0.9561
Risk group*	Low	1585 (98.5)	24 (1.5)		
	Standard/high	764 (95.7)	34 (4.3)	2.62 (1.43 to 4.77)	0.0016
MRD, day 19	Negative	1085 (98.3)	19 (1.7)		
	Positive	1264 (97.0)	39 (3.0)	1.09 (0.58 to 2.10)	0.7825
MRD, day 46†	Negative	2001 (98.3)	35 (1.7)		
	Positive	348 (93.8)	23 (6.2)	3.57 (1.90 to 6.74)	0.0007
Region	High income	1336 (98.1)	26 (1.9)		
	Middle income	765 (97.9)	16 (2.1)	1.11 (0.58 to 2.08)	0.7461
	Low income	248 (93.9)	16 (6.1)	3.70 (1.89 to 7.05)	0.0008

*Initial risk determined at diagnosis.
†Patients without day 46 MRD data were excluded.
MRD, minimal residual disease.

30 June 2018. They also interviewed the parents of the children using a survey form that contained nine items, including the family's annual income, the father's and mother's education and occupation, health insurance coverage, family type (intact vs single parent), type of residence community (rural vs urban) and the number of children (1 vs 2 or more) in the family.

Considering the uneven regional economic development in China, we also sought to interpret results in light of region-specific geographic and socioeconomic contexts. Based on the government-issued report of per capita disposable income (PCDI) in 2016, the average PCDI of each province was calculated, and provinces were considered high-income (upper third PCDI), middle-income (middle-third PCDI), and low-income (lower third PCDI) regions.

Statistical analysis

Associations between categorical variables were tested by the exact (or Fisher's) and Pearson's X^2 procedure. Logistic regression was used to analyse joint effect and independent factors of abandonment. The cumulative incidence of abandonment was estimated by the Kalbfleisch-Prentice method.[16] A p value ≤0.05 was considered to indicate statistical significance; no adjustment of multiple tests was applied. The data were frozen on 30 June 2018 for analysis. All statistical computing was done by the R statistical software V.3.4.4 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/).

RESULTS

From 1 January 2015 to 31 December 2016, a total of 2641 patients with ALL were enrolled in the CCCG-ALL-2015 study. The median age at diagnosis was 4.5 years (range: 3 months to 16.75 years). The median follow-up time was 119 weeks (range: 78.14–182.14 weeks). The 3-year overall survival was 93%. Of the 2641 patients, 83 (3.1%, 95% CI 2.5% to 3.8%) abandoned therapy. The median abandonment rate across the 20 centres was 2.9% (range: 0%–16.5%). The cumulative incidence of treatment abandonment at 50 weeks was 2.8% (0.32% SE), while that for the entire treatment period was 3.2% (0.35% SE; online supplementary figure S2). Of the 83 cases of treatment abandonment, 28 (33.7%) occurred during the window/induction phase, 18 (21.7%) during consolidation treatment, 19 (22.9%) during continuation treatment and 18 (21.7%) during the maintenance phase (online supplementary figure S1); only eight cases developed after week 54. Of the 2641 patients, 990 (37.5%) have completed therapy.

Treatment abandonment was significantly associated with age <1 year or ≥10 years (p=0.0151), standard or high-risk treatment group (p=0.0004), failure to achieve complete remission (p<0.0001), positive MRD at day 19 (p=0.0127) or day 46 (p<0.0001) of remission induction, unfavourable leukaemia genotype (*BCR-ABL1* fusion, *MLL* or *PDGFRB* rearrangement; p=0.0001) and low-income economic region (p<0.0001); it was not associated with gender, central nervous system status, initial white cell count or immunophenotype (table 1). In a multivariate analysis, standard or high-risk treatment group (OR 2.62, 95% CI 1.43 to 4.77; p=0.0016), positive MRD at day 46 (OR 3.57, 95% CI 1.90 to 6.74; p=0.0007) and low-income region (OR 3.70, 95% CI 1.89 to 7.05; p=0.0008) were independent predictions of treatment abandonment (table 2). The abandonment rates in high-income, middle-income and low-income regions were 1.9%, 2.1% and 6.1%, respectively (table 2).

Open-ended interviews of the patients' parents by attending physicians indicated that economic difficulties (42/83, 50.6%) followed by the belief that ALL was incurable (23/83, 27.7%), reactions to the severe side effects of intensive therapy (11/83, 13.3%) and concern over long-term complications (6/83, 7.2%) (table 3) were common reasons. Economic difficulties were considered the main reason for abandonment across the all three income strata (p<0.0001; table 3). Among the 42 families that reported economic difficulties as the main reason for abandonment, 20 (47.6%) were from the region with the lowest PCDI nationwide, and 10 (23.8%) were from Yunnan province, one of the poorest regions in China (p=0.0045; table 4). When we mapped the geographic distribution of families with children that abandoned treatment across the different administrative regions of China (online supplementary figure S3), it was clear that the majority of abandonment cases resided in the low-income regions.

Among the 83 families surveyed, 56 (67.5%) completed the questionnaires. More than two-thirds of the responding parents had less than 9 years of formal education, 94.6% reported household annual incomes below the nationwide 40th percentile (CN¥100 000),[17] 80.4% resided in rural areas, 70% were farmers or blue collar workers and yet only 17.8%

Table 3 Reasons for treatment abandonment in CCCG cooperative centres across economic regions

CCCG cooperative centre number*	Abandonment % (abandoned/treated)	Self-reported economic difficulty, n	Belief of incurability, n	Severe side effects, n	Concerns over long-term complications, n	Religion, n
1	1.2 (4/319)	1	0	2	1	0
2	1.5 (1/68)	1	0	0	0	0
3	1.8 (2/111)	1	1	0	0	0
4	1.8 (3/165)	2	1	0	0	0
5	1.4 (2/147)	1	1	0	0	0
6	0 (0/57)	0	0	0	0	0
7	4.4 (10/224)	1	7	0	2	0
8	1.0 (1/101)	0	0	1	0	0
9	3.8 (11/287)	7	2	1	1	0
10	1.1 (1/89)	0	0	1	0	0
11	2.9 (3/102)	0	2	1	0	0
12	2.4 (2/85)	1	0	1	0	0
13	3.9 (4/104)	4	0	0	0	0
14	3.8 (4/105)	2	0	2	0	0
15	4.5 (3/67)	1	1	0	1	0
16	3.1 (9/291)	5	3	0	1	0
17	0 (0/10)	0	0	0	0	0
18	3.3 (1/30)	0	1	0	0	0
19	3.3 (6/182)	5	0	0	0	1
20	16.5 (16/97)	10	4	2	0	0
P<0.0001†						
High-income† region	2.3 (34/1479)	14	12	4	4	0
Middle-income region	3.1 (26/853)	13	6	5	2	0
Low-income region	7.4 (23/309)	15	5	2	0	1
Total	3.1 (83/2641	50.6 (42/83)	27.7 (23/83)	13.3 (11/83)	7.2 (6/83)	1.2 (1/83) P=0.0001‡

*Centres 1–9, high income, upper third of the average per capita disposable income (PCDI) in 2016; centres 10–17, middle income, middle third of the average PCDI; centres 18–20, low income, lower third of the average PCDI.
†Comparison of abandonment rates across economic regions.
‡Comparisons of reasons for abandonment in three combined economic regions.
CCCG, Chinese Children's Cancer Group.

of the patients were not covered by health insurance (table 5). Patients from families in which the parents had only 9 years or less of education, were farmers or blue collar workers or were unemployed and thus earned less than CN¥50 000 per year were significantly more likely to abandon treatment for economic reasons than were patients from the remaining families; whereas families with more educated parents who had better paid occupations, the patients tended to abandon treatment for non-economic reasons, mainly the lack of belief in cure of ALL (exact X^2 test, $p<0.05$; table 5).

DISCUSSION

The CCCG-ALL-2015 protocol was designed to provide risk-adapted therapy for Chinese children with ALL at 20 participating institutions in different socioeconomic and cultural regions. The study reported here has enrolled about 1250 patients with newly diagnosed ALL annually, representing about 10% of the total 12 000 cases expected nationwide over the same period.[18] This large patient cohort and its broad geographic and socioeconomic distribution allowed us to address the frequency of treatment abandonment and its contributing factors with statistical confidence.

The cumulative 3.2% incidence of abandonment in this study is relatively low compared with those from other economically challenged countries which ranged from 20% to 50%.[6 7 10] Until recently, refusal or abandonment of paediatric cancer treatment had been a common occurrence in China. Due to the complexity and cost of ALL therapy and uncertainties about survival, as well as acute and long-term sequelae, the refusal or abandonment of treatment was a culturally embraced alternative. In a previous single institution study conducted by SCMC, of the 234 children with ALL treated between October 1998 and June 2003, a total of 66 (28%) (most of whom were not citizens of Shanghai) had to abandon treatment for financial reasons.[19] In this period, it was estimated that only about 30% of cases of paediatric cancer were treated with curative intent in China.[11] However, this situation has changed dramatically as demonstrated by the findings of our study. The reasons for this reversal can be traced to 1978 when the government of China introduced economic reforms to a free-market system. Sustained economic productivity greatly expanded as did the average net household income and personal expenditures. Following the outbreak of severe acute respiratory syndrome in 2003, China developed an ambitious health reform plan. The total health expenditure increased from CN¥74.7 billion in 1990 to CN¥1998 billion in 2010, and average per-person health expenditure from CN¥65.4 in 1990 to CN¥1490.1 in 2010.[20] The reform was intended to expand insurance coverage to about 90% of the population, establish a national essential medicines programme, improve the primary care services, provide basic healthcare and manage referrals to specialist care and hospitals. These included the NRCMS, a community-based health insurance that was introduced in China to increase access to healthcare services for individuals with low incomes.[21] By June 2012, a total of 812 million people

Table 4 Distribution income region of 42 patients who abandoned therapy due to economic difficulties

Patients' home residence	Income level*	2016 GDP per capita† (CN¥)	2016 PCDI (CN¥)	Abandoned treatment because of economic difficulties (%)	
Hong Kong	High	289 928	153 920	0	
Shanghai	High	116 562	54 305	0	
Zhejiang	High	84 916	38 529	0	
Tianjin	High	115 053	34 074	0	
Jiangsu	High	96 887	32 070	1 (2.4)	
Guangdong	High	74 016	30 296	3 (7.1)	
Fujian	Middle	74 707	27 608	1 (2.4)	
Shandong	Middle	68 733	24 685	3 (7.1)	
Inner Mongolia	Middle	72 064	24 127	1 (2.4)	
Chongqing	Middle	58 502	22 034	5 (11.9)	
Hubei	Middle	55 665	21 787	4 (9.5)	
Hunan	Middle	46 382	21 115	0	
Jiangxi	Middle	40 400	20 110	2 (4.8)	
Anhui	Middle	39 561	19 998	1 (2.4)	
Heilongjiang	Middle	40 432	19 838	1 (2.4)	
Hebei	Low	43 062	19 725	3 (7.1)	
Shanxi	Low	35 532	19 049	1 (2.4)	
Shaanxi	Low	51 015	18 874	0	
Sichuan	Low	40 003	18 808	5 (11.9)	
Yunnan	Low	31 093	16 720	10 (23.8)	
Gansu	Low	27 643	14 670	1 (2.4)	
Abandonment rate					
High-income regions				4 (9.5)	P=0.0045‡
Middle-income regions				18 (42.8)	
Low-income regions				20 (47.6)	

The average exchange rate in June 2018 was US$1=CN¥6.7.
*High income, upper third of the average per capita disposable income (PCDI) in 2016 for each province; middle income, middle third of the average PCDI; low income, lower third of the average PCDI.
†2016 economic statistics released by the National Bureau of Statistics (NBS).
‡For comparison of abandonment rates across three income regions.
GDP, gross domestic product.

nationwide were covered by the NRCMS, accounting for 95% of the entire rural population. The reimbursement rate exceeded 75% for hospitalisation expenses and 50% for clinical visits.[22 23] In 2010, the NRCMS began to cover most of the treatment expenses of childhood ALL.[24] Altogether, these measures have contributed to a much lower rate of treatment abandonment and are consistent with the observation that government expenditures on health are significantly associated with improved survival in ALL in countries with limited resources. In the study conducted by the Children's Hospital of Soochow University in Jiangsu province, the investigators evaluate the influence of government medical policies on reducing abandonment of treatment in patients with paediatric ALL. They reported an abandonment rate of 50% (8 of 16) between 2002 and 2005, and 20% (15 of 75) between 2006 and 2012. The results of their study concluded that government-funded healthcare expenditure programmes reduced families' economic burden and thereby reduced the abandonment rate with resultant increased survival.[24]

In this study, abandonment occurred mostly in the early treatment phases, and only rarely after 1 year. However, the frequency of abandonment varied among participating institutions, from zero to 16.5%. These initial observations suggested that the different sociocultural and economic characteristics of the regions where the institutions are located might be associated with treatment abandonment, and thus could impact efforts to identify patients at risk for this dire outcome.

Indeed, we found that low-income regions, both standard and high-risk treatment groups and the presence of MRD were independently associated with abandonment. These data are consistent with the findings of our survey of 83 families in which a child had abandoned treatment. The most common reason for abandonment, economic difficulties, was reported by 50.6% of the families, 94% of whom had annual household incomes below CN¥100 000, a proportion considerably higher than the national average of less than 40%.[17] Importantly, a high proportion of the families reporting economic difficulty as the chief reason for treatment abandonment resided in the Yunnan province, one of the poorest and ethnically diverse regions of China.

The belief that leukaemia is incurable, reported by 27.7% of the respondents, was the second most common reason for abandonment, while severe side effects, religious faith and concerns over long-term side effects accounted for the remaining cases. These findings are consistent with previous studies indicating that abandonment rates markedly decrease when economic and educational support are provided to families with a child with cancer.[25 26] Hence, treatment abandonment should be considered a preventable cause of treatment failure in ALL.

Table 5 Reasons for treatment abandonment from questionnaires

Characteristics	Category	n (%)	Reasons for treatment abandonment				P value*
			Self-reported economic difficulty n (%)	Belief of incurability n (%)	Experience of severe side effects n (%)	Concern over long-term complications n (%)	
Father's education†	≤9 years	33 (63.5)	23 (69.7)	4 (12.1)	5 (15.2)	1 (3.0)	0.0026
	10–12 years	12 (23.1)	3 (25.0)	6 (50.0)	3 (25.0)	0 (0)	
	>12 years—university	7 (13.4)	1 (14.3)	2 (28.6)	2 (28.6)	2 (28.6)	
Mother's education	≤9 years	44 (78.6)	27 (61.4)	7 (15.9)	8 (18.2)	2 (4.5)	0.0068
	10–12 years	7 (12.5)	2 (28.6)	4 (57.1)	1 (14.3)	0 (0)	
	>12 years—university	5 (8.9)	0 (0)	2 (40.0)	1 (10.0)	2 (40.0)	
Father's occupation†	Unemployed	1 (1.9)	1 (100)	0 (0)	0 (0)	0 (0)	0.3473
	Blue collar worker	13 (25.0)	7 (53.8)	3 (23.0)	2 (15.4)	1 (7.8)	
	Farmer	27 (51.9)	17 (63.0)	5 (18.5)	4 (14.8)	1 (3.7)	
	Small shop owner/vendor	6 (11.5)	1 (16.7)	2 (33.3)	3 (50.0)	0 (0)	
	Office staff	5 (9.6)	1 (20.0)	2 (40.0)	1 (20.0)	1 (20.0)	
Mother's occupation	Unemployed	13 (23.2)	6 (46.2)	5 (38.5)	2 (15.4)	0 (0)	0.0281
	Blue collar worker	7 (12.5)	5 (71.4)	1 (14.3)	0 (0)	1 (14.3)	
	Farmer	29 (51.8)	18 (62.1)	5 (17.2)	5 (17.2)	1 (3.4)	
	Small shop owner/vendor	2 (3.6)	0 (0)	1 (50.0)	1 (50.0)	0 (0)	
	Office staff	5 (8.9)	0 (0)	1 (20.0)	2 (40.0)	2 (40.0)	
Annual family income (CN¥)‡	>100 000	3 (5.4)	1 (33.3)	1 (33.3)	0 (0)	1 (33.3)	0.0305
	50 000–100 000	9 (16.1)	3 (33.3)	2 (22.2)	2 (22.2)	2 (22.2)	
	30 000–50 000	24 (42.9)	9 (37.5)	8 (33.3)	6 (25.0)	1 (4.2)	
	<30 000	20 (35.7)	16 (80.0)	2 (10.0)	2 (10.0)	0 (0)	
Type of residence/community	Urban	11 (19.6)	3 (27.3)	4 (36.4)	2 (18.2)	2 (18.2)	0.1234
	Rural	45 (80.4)	26 (57.8)	9 (20.0)	8 (17.8)	2 (4.4)	
Health insurance	Yes (coverage >50%)	14 (25.0)	5 (35.7)	7 (50.0)	1 (7.1)	1 (7.1)	0.0700
	Yes (coverage 31%–50%)	16 (28.6)	7 (43.8)	2 (12.5)	5 (31.2)	2 (12.5)	
	Yes (coverage ≤30%)	16 (28.6)	10 (62.5)	4 (25.0)	1 (6.3)	1 (6.3)	
	No	10 (17.8)	7 (70.0)	0 (0)	3 (30.0)	0 (0)	
Number of siblings	One	21 (37.5)	9 (42.9)	6 (28.6)	4 (19.0)	2 (9.5)	0.7183
	Two or more	35 (62.5)	20 (57.1)	7 (20.0)	6 (17.1)	2 (5.7)	
Family type	Both parents	52 (92.9)	27 (51.9)	12 (23.1)	10 (19.2)	3 (5.8)	0.4150
	Single parent	4 (7.1)	2 (50.0)	1 (25.0)	0 (0)	1 (25.0)	

*P values were calculated by exact X^2 test.
†In all four single-parent families, father's education and occupation information was missing.
‡Report from the Shanghai Academy of Social Sciences in 2016 shows fewer than 40% of all households in China with an annual income below CN¥100 000.[17]

Although by themselves economic constraints were highly associated with abandonment, we considered that other factors might have contributed to the impact of this finding. This perception led to an analysis of demographic and cultural variables that defined families in which a child had abandoned treatment. Indeed, a complex socioeconomic and cultural profile emerged in these families, including a reduced number of years of formal education, a high frequency of farmers residing in rural areas, low family income and health insurance covering less than 50% of the patient's medical expenses (table 5). Thus, for patients with a persistent disease at the end of induction therapy, one could predict that in addition to a low family income, this unfavourable profile would greatly increase the likelihood of treatment rejection.

There are other considerations to decrease abandonment rates particularly in families still residing in rural areas and rural-to-urban migrant families who are not insured, although the lack of this information is a limitation of this study. Providing support for housing, transportation, food and universal medical insurance has been associated with reductions in abandonment in Central and South America.[15] In some Chinese provinces, medical insurance policies specify that the family must pay the expenses upfront and seek reimbursement later. However, many low-income families cannot afford to pay even the initial medical bills. Thus, community support groups could be organised to provide financial support to economically vulnerable families who require medical treatment. The government could also revise the policy requiring upfront payment of medical expenses. The persistence of a small percentage of patients who abandoned therapy despite economic support suggests that interventions in parental education and psychosocial guidance are also needed to minimise this complication.

CONCLUSIONS

Treatment abandonment by paediatric patients with ALL has decreased remarkably in most institutions in China. Universal medical insurance for these children and increased government spending on health are the main reasons for this success. Extending these societal benefits to impoverished rural regions, internal migrant populations and other paediatric cancers will require additional strategies.

Author affiliations
[1]Department of Hematology/Oncology, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Key Lab of Pediatric Hematology and Oncology of China Ministry of Health, and National Children's Medical Center, Shanghai, China
[2]Department of Hematology/Oncology, Chongqing Medical University Affiliated Children's Hospital, Chongqing, China
[3]Department of Pediatrics, Institute of Hematology and Blood Disease Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China
[4]Department of Hematology/Oncology, Children's Hospital of Soochow University, Suzhou, China
[5]Department of Pediatrics, West China Second University Hospital of Sichuan University, Chengdu, China
[6]Department of Hematology/Oncology, Guangzhou Women and Children's Health Care Center, Guangzhou, China
[7]Department of Pediatrics, Southern Medical University Affiliated Nanfang Hospital, Guangzhou, China
[8]Department of Hematology/Oncology, Nanjing Children's Hospital Affiliated to Nanjing Medical University, Nanjing, China
[9]Department of Hematology/Oncology, Jiangxi Provincial Children's Hospital, Nanchang, China
[10]Department of Pediatrics, Qilu Hospital of Shandong University, Jinan, China
[11]Department of Hematology/Oncology, Kunming Children's Hospital, Kunming, China
[12]Department of Hematology/Oncology, Children's Hospital of Fudan University, Shanghai, China
[13]Department of Pediatrics, Huazhong University of Science and Technology Tongji Medical College Union Hospital, Wuhan, China
[14]Department of Pediatrics, Huazhong University of Science and Technology Tongji Medical College Tongji Hospital, Wuhan, China
[15]Department of Pediatrics, Anhui Medical University Second Affiliated Hospital, Hefei, China
[16]Department of Hematology/Oncology, Children's Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China
[17]Department of Pediatrics, Qingdao University Affiliated Hospital, Qingdao, China
[18]Deparment of Paediatrics, The Chinese University of Hong Kong, Shatin, Hong Kong
[19]Department of Hematology/Oncology, Northwest Women's and Children's Hospital, Xi'an, China
[20]Department of Pediatrics, Xiangya Hospital Central South University, Changsha, Hunan, China
[21]Department of Biostatistics, St Jude Children's Research Hospital, Memphis, Tennessee, USA
[22]Department of Oncology, St Jude Children's Research Hospital, Memphis, USA

Acknowledgements We are grateful for support from St Jude Global Pediatric Medicine programme and VIVA-China Children's Cancer Foundation.

Contributors JC, SS, JT and CHP had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. JC, SS, CC, CHP and JT designed the research study. JC, SS, RCR, CHP and JT wrote the paper. JC and CC analysed the data. Critical revision of the manuscript for important intellectual content was reviewed, edited and revised by all authors.

Funding Funding for this work was provided by the NCI grant CA21765, the National Natural Science Foundation of China (No 81670136, to JT) and the American Lebanese and Syrian Associated Charities (ALSAC).

Disclaimer The funding agencies had no role in the conduct, design, data collection, analysis and interpretation of the study, or in writing the report. The corresponding author had the final responsibility for submission of the manuscript for publication.

Competing interests None declared.

Patient consent Parental/guardian consent obtained.

Ethics approval The study was approved by the Institutional Review Board of each participating institution.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data sets used and/or analysed during the current study are available on reasonable request by writing to caijiaoyang@scmc.com.cn.

REFERENCES

1 Pui CH, Yang JJ, Hunger SP, *et al*. Childhood Acute Lymphoblastic Leukemia: Progress Through Collaboration. *J Clin Oncol* 2015;33:2938–48.
2 Pui CH, Yang JJ, Bhakta N, *et al*. Global efforts toward the cure of childhood acute lymphoblastic leukaemia. *Lancet Child Adolesc Health* 2018;2:440–54.
3 Ribeiro RC, Steliarova-Foucher E, Magrath I, *et al*. Baseline status of paediatric oncology care in ten low-income or mid-income countries receiving My Child Matters support: a descriptive study. *Lancet Oncol* 2008;9:721–9.
4 Nassin ML, Mueller EL, Ginder C, *et al*. Family Refusal of Chemotherapy for Pediatric Cancer Patients: A National Survey of Oncologists. *J Pediatr Hematol Oncol* 2015;37:351–5.
5 Wang C, Yuan XJ, Jiang MW, *et al*. Clinical characteristics and abandonment and outcome of treatment in 67 Chinese children with medulloblastoma. *J Neurosurg Pediatr* 2016;17:49–56.
6 Weaver MS, Arora RS, Howard SC, *et al*. A practical approach to reporting treatment abandonment in pediatric chronic conditions. *Pediatr Blood Cancer* 2015;62:565–70.
7 Siddiqui DE, Ashraf MS, Iftikhar S, *et al*. Predictors of treatment abandonment for patients with pediatric cancer at Indus Children Cancer Hospital, Karachi, Pakistan. *Pediatr Blood Cancer* 2018;65:e26818.
8 Rossell N, Challinor J, Gigengack R, *et al*. Choosing a miracle: Impoverishment, mistrust, and discordant views in abandonment of treatment of children with cancer in El Salvador. *Psychooncology* 2017;26:1324–9.
9 Fuentes-Alabi S, Bhakta N, Vasquez RF, *et al*. The cost and cost-effectiveness of childhood cancer treatment in El Salvador, Central America: A report from the Childhood Cancer 2030 Network. *Cancer* 2018;124:391–7.
10 Mostert S, Sitaresmi MN, Gundy CM, *et al*. Influence of socioeconomic status on childhood acute lymphoblastic leukemia treatment in Indonesia. *Pediatrics* 2006;118:e1600–e1606.
11 Wang YR, Jin RM, Xu JW, *et al*. Treatment refusal and abandonment in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 2011;28:249–50.

12 Li Y, Wu Q, Liu C, *et al*. Catastrophic health expenditure and rural household impoverishment in China: what role does the new cooperative health insurance scheme play? *PLoS One* 2014;9:e93253.
13 Pui CH, Campana D, Pei D, *et al*. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med* 2009;360:2730–41.
14 Liu Y, Chen J, Tang J, *et al*. Cost of childhood acute lymphoblastic leukemia care in Shanghai, China. *Pediatr Blood Cancer* 2009;53:557–62.
15 Arora RS, Eden T, Pizer B. The problem of treatment abandonment in children from developing countries with cancer. *Pediatr Blood Cancer* 2007;49:941–6.
16 Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. 2nd Edition. Hoboken, NJ: Wiley-Interscience, 2002:254–5.
17 Li P, Zhu D. Make Efforts to Develop an Olive-shaped Distribution Pattern: An Analysis Based on Data from the Chinese Social Survey for 2006-2013. *Social Sciences in China* 2016;37:5–24.
18 Bao P, Wu C, Gu K, *et al*. [Incidence trend of malignant tumors in children in Shanghai]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2016;37:106–10.
19 Tang JY, Xue HL, Gu LJ, *et al*. [Failure of treatment and protocol compliance in patients with acute lymphoblastic leukemia]. *Zhonghua Er Ke Za Zhi* 2005;43:490–3.
20 Tang S, Tao J, Bekedam H. Controlling cost escalation of healthcare: making universal health coverage sustainable in China. *BMC Public Health* 2012;12 Suppl 1(Suppl 1):S8.
21 Yip WC, Hsiao WC, Chen W, *et al*. Early appraisal of China's huge and complex health-care reforms. *Lancet* 2012;379:833–42.
22 Marten R, McIntyre D, Travassos C, *et al*. An assessment of progress towards universal health coverage in Brazil, Russia, India, China, and South Africa (BRICS). *Lancet* 2014;384:2164–71.
23 Zhi-Ruo Z, Jian-Qing MI, Long-Jun GU, *et al*. Using sound clinical paths and diagnosis-related Groups (DRGs)-based payment reform to bring benefits to patient care: A case study of leukemia therapy. *Front. Med. China* 2010;4:8–15.
24 Zhou Q, Hong D, Lu J, *et al*. Pediatric medical care system in china has significantly reduced abandonment of acute lymphoblastic leukemia treatment. *J Pediatr Hematol Oncol* 2015;37:181–4.
25 Caruso Brown AE, Slutzky AR. Refusal of treatment of childhood cancer: A systematic review. *Pediatrics* 2017;140:e20171951.
26 Ghatak N, Trehan A, Bansal D. Financial burden of therapy in families with a child with acute lymphoblastic leukemia: report from north India. *Support Care Cancer* 2016;24:103–8.