BMJ Open

Adherence to childhood cancer treatment: a prospective cohort study from Northern Vietnam

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ABSTRACT

Objectives Global incidence and attention to childhood cancer is increasing and treatment abandonment is a major cause of treatment failure in low- and middle-income countries. The purpose of this study was to gain an understanding of factors contributing to non-adherence to treatment.

Design A prospective cohort study with 2 year follow-up of incidence, family-reported motives and risk factors.

Setting The largest tertiary paediatric oncology centre in Northern Vietnam.

Participants All children offered curative cancer treatment, from January 2008 to December 2009.

Primary and secondary outcome measures Family decision to start treatment was analysed with multivariable logistic regression, and family decision to continue treatment was analysed with a multivariable Cox model. This assessment of non-adherence is thereby methodologically consistent with the accepted definitions and recommended practices for evaluation of treatment abandonment.

Results Among 731 consecutively admitted patients, 677 were eligible for treatment and were followed for a maximum 2 years. Almost half the parents chose to decline curative care (45.5%), either before (35.2%) or during (10.3%) the course of treatment. Most parents reported perceived poor prognosis as the main reason for non-adherence, followed by financial constraints and traditional medicine preference. The odds of starting treatment increased throughout the study-period (OR 1.04 per month (1.01 to 1.07), p=0.002), and were independently associated with prognosis (OR 0.51 (0.41 to 0.64), p=<0.0001) and travel distance to hospital (OR 0.998 per km (0.996 to 0.999), p=0.004). The results also suggest that adherence to initiated treatment was significantly higher among boys than girls (HR 1.69 (1.05 to 2.73), p=0.03).

Conclusions Non-adherence influenced the prognosis of childhood cancer, and was associated with cultural and local perceptions of cancer and the economic power of the affected families. Prevention of abandonment is a prerequisite for successful cancer care, and a crucial early step in quality improvements to care for all children with cancer.

INTRODUCTION

Low- and middle-income countries have approximately 5% of the global resources to treat and prevent cancer, but 80% of the global cancer disease burden.[1] This inequitable distribution implies a prevailing perception of cancer care as insignificant, impossible

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Strengths and limitations of this study

► A large prospective cohort study with a 2-year follow-up of consecutive children with cancer in Northern Vietnam.
► Incidence and risk factors of adherence to treatment were measured for all children.
► For family-reported motives, there was 90.8% response rate among families not starting treatment and 62.9% among families not continuing treatment.

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or inappropriate in developing countries.[2] However, both incidence of and attention to childhood cancer is now increasing also outside high-income settings.[3 4]

Every year approximately 271 000 children worldwide develop cancer.[5 6] Currently about 90% of paediatric cancer deaths occur in low- and middle-income countries,[7] but the contribution of childhood cancer to child mortality in these settings has long escaped wider public attention.[8–10] As fewer children succumb to infectious diseases of infancy and childhood, and countries experience demographical and epidemiological shifts, the relative importance of morbidity and mortality from childhood cancer and other non-communicable diseases will increase. Childhood cancer has ranked among the top 10 causes of death in low-income countries, and top five causes of death in middle-income countries, for children aged 5 to 14 years.[2 11] In high-income countries, cancer is the leading cause of death from disease among children and adolescents.[12] The number of children in the world with cancer is projected to increase by 30% by 2020, and the global cancer divide will widen.[7]

Vietnam has recently emerged from a low-income to a lower middle-income country, and is renowned for achieving health outcomes far beyond its income level.[13] As a consequence of its successes, the healthcare system is now increasingly challenged by cancer

and other non-communicable diseases, and is starting to adapt to new population needs. In 2006, Vietnam had a postulated overall event-free 5 year survival from childhood cancer[14] measuring about a 10th compared with the current 80% in high-income countries.[15–17] With the aim of assisting the national development of paediatric oncology, the Lund Vietnam Childhood Cancer Program was inaugurated in January 2008.

There are many reasons why children with cancer die undiagnosed or untreated in low- and middle-income countries, for example, shortage of trained human resources, insufficient infrastructure, low diagnostic capabilities, poor referral systems, inconsistent drug availability and lack of supportive care.[11 18 19] Children present in advanced stages of their disease, with malnutrition and other comorbidities, and the treatment is complex and toxic.[20] Patients and their families are sensitive to both direct and hidden costs of treatment and disease.[7 18 21] In high-income countries, non-adherence to treatment is extremely rare,[22 23] but in developing countries non-adherence is a major determinant of childhood cancer survival, and consistently the most common cause of treatment failure.[20 22 24] Indeed, the annual number of abandonment events in low- and middle-income countries is nearly equivalent to the total number of new childhood cancer cases in high-income settings.[22]

Recognising why parents choose to decline cancer treatment is essential to increase paediatric cancer survival. However, no prospective analysis has yet reported of adjusted risk factors for both failure to start treatment and failure to continue childhood cancer treatment. The purpose of this study was to gain an understanding of factors contributing to adherence to treatment, and to determine the cumulative incidence of non-adherence. Over 4 years we prospectively measured the incidence, motives and risk factors for non-adherence among children with cancer at the largest tertiary paediatric oncology centre in Northern Vietnam. Based on previous literature and conclusions from initial qualitative interviews with parents and staff, our hypothesis was that adherence to treatment was associated with poor prognosis, poverty and long travel distance to the hospital, and that adherence to treatment would increase after the initiation of the collaborative programme.

METHODS
Study design and study subjects
We conducted a prospective cohort study of children offered curative cancer treatment at the main referral hospital of paediatric oncology in Northern Vietnam: the National Hospital of Pediatrics (Bệnh viện Nhi Trung Ương) in Hanoi. All 731 consecutive patients younger than 15 years admitted to the department of paediatric oncology from January 2008 to December 2009 were included in the study. Central nervous system (CNS) tumours and retinoblastomas were not represented in this cohort, since they were treated in another department of
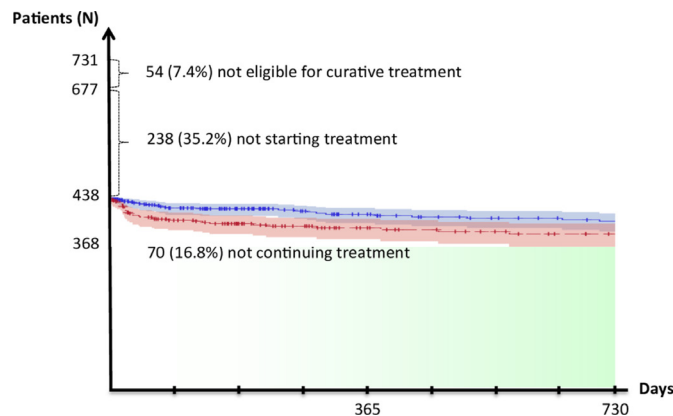

Figure 1 Adherence to treatment among children diagnosed with cancer at the paediatric oncology ward, National Hospital of Pediatrics in Hanoi, 2008 to 2009. Stratified by gender (boys blue, girls red). Log-rank p=0.028.

the hospital. Patients not offered cancer treatment with the intention of cure were excluded from further analysis (figure 1), as were patients curable with surgery-only strategies, not requiring multimodal treatment (ganglioneuroblastoma, localised low-grade gonadoblastoma, mesoblastic nephroma, pheochromocytoma and mature teratoma).

Each patient was followed for a maximum of 2 years from the start of chemotherapy. The date of therapeutic surgery was used as the starting date if surgery was performed before chemotherapy and if malignant diagnosis was available prior to surgery. The date of diagnosis was used as the starting date if the date of first therapeutic treatment was missing. Children were eligible for analysis as long as they were offered curative cancer treatment, and patients were censored at the time of death, at the time of referral to other health facilities or when curative treatment was either completed or no longer offered. The Lund Vietnam Childhood Cancer Program did not support patients and families financially.

Definitions and criteria
The primary outcome was adherence to cancer treatment prescribed with the intention to cure. Non-adherence is more commonly known as treatment abandonment, which is defined by the International Society of Pediatric Oncology as 1. Failure to start prescribed curative cancer treatment, or 2. Failure to continue such treatment, resulting in either premature termination of treatment or a hiatus of four or more weeks in scheduled treatment.[25] In this study, we considered abandonment and non-adherence to be identical. The term abandonment has an accusatory connotation in Vietnam, and was avoided. Failure to start treatment occurred per definition on day 0. Failure to continue treatment could occur at any given time from start of treatment to censoring, and this endpoint was therefore connected to a time-to-event. We considered terminally ill children as non-eligible for curative therapy, unable to abandon treatment while in their last week of life.

Tumour related prognosis was graded into three categories based on tumour type, age, grade and stage (online supplementary appendix A). To assess changes over the course of the study, a time variable was computed as the interval between date of diagnosis and the baseline of 1 January, 2008, when the Lund Vietnam Childhood Cancer Program started in Hanoi. Travel distance to the National Hospital of Pediatrics was measured in kilometres. The regional capture rate was defined as the percentage of observed paediatric cancer cases referred, diagnosed and admitted from the patients' respective region of origin, compared with the expected number of cancer cases in this region. This proportion was used as a proxy for paediatric oncology capacity at the patients' regional level, and was determined for each of the 30 regions of Northern Vietnam by combining age-specific population data from the Vietnamese census of 2009[26 27] and a paediatric cancer incidence (excluding CNS tumours and retinoblastoma) of 107 per million[28 29](online supplementary appendix B). Family socioeconomic status was not measured.

Data collection and validation

Patient data were prospectively entered, maintained and continuously validated by a designated data manager at the department of oncology at the National Hospital of Pediatrics. The role of the data manager was also to contact families over phone in case of non-adherence. Families who prematurely left the hospital could phrase their own motives for non-adherence, without being limited to a certain selection or certain number of choices. The data manager captured these responses as free text in the database, and the motives were then aggregated into categories by consensus of two researchers, and quantified. The response rate was 90.8% among those not starting treatment, and 62.9% among those not continuing treatment. No additional validation or review of medical files was performed as part of this study. The database was established on January 2008 through the Lund Vietnam Childhood Cancer Program. The study was reviewed and approved by the Biomedical Research Ethics Committee of the National Hospital of Pediatrics, Hanoi.

Data analyses

Descriptive statistics were computed for each study variable. Mean with 95% CIs was used for normally distributed continuous variables, and median with IQR when variables were not normally distributed. Two multivariable models assessed factors associated with adherence to treatment:

Decision to start treatment: A multivariable logistic regression model established covariate ORs for the binary decision to *start* treatment. Unadjusted, univariate logistic regression was performed for initial exploration. Covariates were included in the final model regardless of univariate association, and univariate ORs were not reported. With 238 events, the model was stable for the inclusion of all six covariates.

All continuous covariates were kept linear in the multivariable model, after first ensuring linearity by dividing the range of numerical values into five equal bins, assessing for stepwise monotonous increases in log odds. For the sake of clarity, continuous variables were also dichotomised for stratified display of adherence proportions. Travel distance and regional capture rate were hereby split at the median. Age was split at the age of 6 years, since patients younger than 6 years in Vietnam receive more comprehensive national health insurance.

Decision to continue treatment: A multivariable Cox model established covariate HRs for the time-sensitive binary decision to *continue* treatment. With 70 events, the model was stable for the inclusion of all six covariates. There were no departures from the proportional hazard assumptions for the model when assessing with supremum test for proportional hazards assumption and martingale residuals (online supplementary appendix C). Time to non-adherence events was also displayed using the Kaplan-Meier method with 95% CIs and log-rank tests.

Alpha was set at 0.05. Statistical software SAS V.9.3 (SAS Institute Inc, Cary, North Carolina, USA) was used for statistical analyses.

Patient and public involvement

The research question, outcome measures and study design were developed without the active involvement of patients and the public.

RESULTS

During the study interval, 677 children were eligible for curative cancer treatment. Acute lymphocytic leukaemia (ALL) was the most common diagnosis, affecting 270 (39.9%) of the diagnosed children. Prognosis was defined as 'favourable' in about a quarter of all cancer cases (25.4%), and 'poor' in over a third (37.7%). More than half of the patients were boys (58.3%).

Median age at diagnosis was 3.62 years (IQR 1.63 to 7.67), and two-thirds (66.0%) of the children were younger than 6 years of age when diagnosed with cancer. Median travel distance between home and hospital was 99.6 km (IQR 47.1 ot 164). Patient characteristics are summarised in table 1.

Adherence to treatment was maintained for 369 children (54.5%), while parents declined curative treatment in 238 cases (35.2%), and discontinued commenced treatment in 70 cases (10.3%). Failure to continue treatment was particularly common during the initial phases of treatment, but could happen at any time during the course of treatment (figure 1). Among the patients who failed to *continue* treatment, the median time to adherence failure was 32 days (IQR 15 to 182) (online supplementary appendix D).

Perceived poor prognosis was the most commonly reported reason not to start (55%) or not to continue (23%) curative cancer treatment, followed by financial difficulties and traditional medicine preference. Travel

Table 1 Study variables and descriptive statistics of children offered curative cancer treatment at National Hospital of Pediatrics, 2008 to 2009

	n	%
Year of diagnosis (n=677)		
2008	345	51.0
2009	332	49.0
Gender (n=677)		
Male	395	58.3
Female	282	41.7
Age (n=654)		
Median years (IQR)	3.62 (1.63 to 7.67)	
Prognosis (n=677)		
Favourable	172	25.4
Intermediate	250	36.9
Poor	255	37.7
Diagnosis (n=677)		
ALL	270	39.9
AML	108	16.0
Unspecified leukaemia	17	2.5
Neuroblastoma	79	11.7
Germ cell tumours	47	6.9
Non-Hodgkin's lymphoma	34	5.0
Wilms tumours	31	4.6
Liver cancer	29	4.3
Soft tissue sarcoma	23	3.4
Non-Wilms kidney tumours	12	1.8
Hodgkin's lymphoma	9	1.3
Ewing sarcoma	7	1.0
Osteosarcoma	4	0.6
Other tumours	7	1.0
Travel distance (n=671)		
Median km (IQR)	99.6 (47.1 to 164)	
Regional capture rate (n=670)		
Mean % (95% CI)	39.0 (38.2 to 39.8)	

ALL, acute lymphocytic leukaemia; AML, acute myelocytic leukaemia; km, kilometre.

distance was of minor reported importance (figure 2). Parents and physicians usually had congruent views of prognosis, but 26.1% of the 130 patients who did not start treatment due to disbelief in cure had indeed a favourable or intermediate prognosis (table 2).

The adjusted odds of *starting* treatment increased significantly over the course of the study (OR 1.04 per month (1.01 to 1.07), p=0.002) (table 3). The odds of *starting* treatment also significantly declined with poorer prognosis (OR 0.51 (0.41 to 0.64), p=<0.0001) and increasing travel distance (OR 0.996 per km (0.996 to 0.999), p=0.004) (table 3). The relative influence of non-adherence risk factors varied over the course of treatment (table 3). Girls were less likely than boys to adhere to ongoing curative cancer treatment (log-rank, p=0.028) (figure 1), and had a significantly higher adjusted HR of *not continuing* treatment (HR 1.69 (1.05 to 2.73), p=0.03) (table 3). Non-adherence per tumour diagnosis is presented in online supplementary appendix E.

DISCUSSION

This large prospective cohort study measured incidence, motives and factors associated with adherence to treatment among children with cancer in Northern Vietnam, 2008 to 2009. Almost half the parents chose to decline curative care (45.5%), either before (35.2%) or during (10.3%) the course of treatment. Even when chances of survival were higher, most parents reported perceived poor prognosis as the main reason for non-adherence, followed by financial constraints and traditional medicine preference. Risk factors for non-adherence changed over the course of treatment, and our results support the hypothesis that adherence to *start* treatment increased throughout the study-period, and that it was independently associated with both prognosis and travel distance to hospital. The results also suggest that adherence to *initiated* treatment may be significantly higher among boys than girls.

Our study offers the chance to analyse non-adherence over time: how risk factors for not starting treatment were different from risk factors for not continuing treatment. This trend may illustrate how each treatment phase involves its own challenges, but could also reflect how less influential risk factors become increasingly detectable as more influential risk factors have had their effects.

Adherence rates

Our finding that non-adherence was a major cause of treatment failure for paediatric cancer is congruent with previous reports from low- and middle-income countries.[20 24 30] The wide intervals of published adherence rates reflect vast global disparities in paediatric oncological care, differences in patient populations, geography, health systems and financial support,[18 22] but also inconsistent definitions.[31] Many previous studies have included only abandonment from *commenced* treatment, not refusal to *start* treatment, which in our setting was the considerably larger group. This is well illustrated in a review of Chinese patients diagnosed with ALL: 53.6% refused to start treatment and another 10.8% prematurely discontinued treatment.[32] Most publications present stratified incidence statistics, often based on relatively small samples sizes and select cancer forms. Some studies also survey motives why parents choose not to adhere to treatment,[24 32–35] or assess for risk factors among patient characteristics.[20 30]
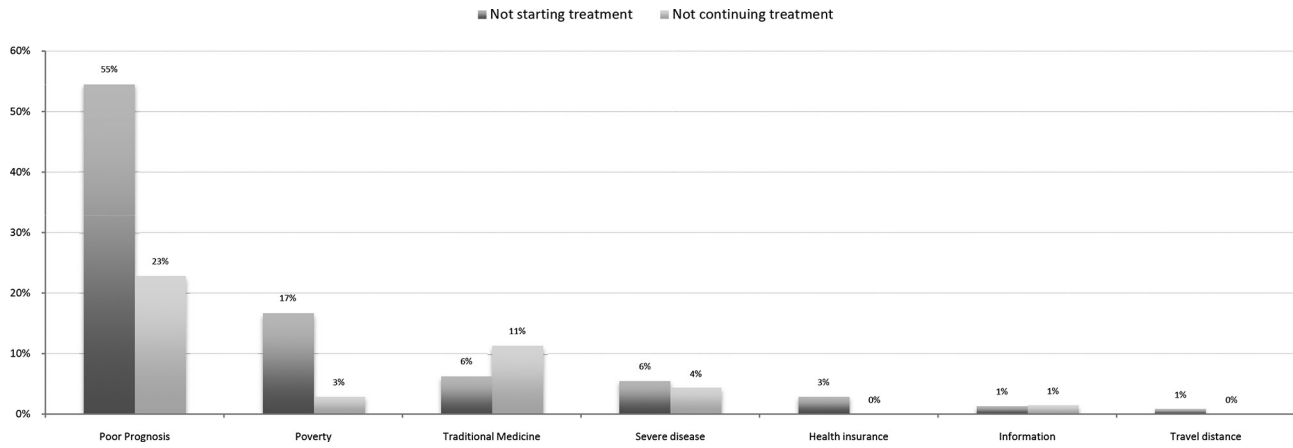
Figure 2 Proportions of patients that report a certain motive for not starting treatment (dark grey) or not continuing treatment (light grey). Not limited to one choice per patients. 90.8% response rate for the 238 patients that did not start treatment (210 motives reported), 62.9% response rate for the 70 patients not continuing treatment (30 motives reported).

Motives

Expert opinions,[18 36–39] qualitative studies[24 34 40] and semi-structured interviews[32 33 35 41 42] have acknowledged that multiple medical and socioeconomic factors make parents decline curative cancer treatment for their child. Our finding that non-adherence primarily is due to futility and financial constraints are in line with these previous studies. A well-powered study in Indonesia, that surveyed parents at home after not starting or not continuing ALL treatment, highlighted poverty and perceived poor prognosis as equally important for adherence, followed by treatment side effects, transportation difficulties and that children did not want to be a burden for the family.[33] More than half of the parents had lost their job as a consequence of their child's disease, many had to sell property such as house and land, and more than half of the families were still indebted years after the child had left the hospital.[33] In a hospital study from Malawi, both direct and indirect costs were of significance for adherence to treatment.[41] Interestingly, a quarter of all patients in our study who reported non-adherence due to perceived poor prognosis, had cancer with favourable or intermediate prognosis. Our study is the first to correlate clinical data to given motives, and our results suggest that addressing parental beliefs about cancer,

through education and clinical excellence, has the potential to increase adherence.

Risk factors

Non-adherence to treatment is associated with certain patient characteristics, and identification of these risk factors can also point towards causal mechanisms and facilitate targeted interventions. Confounding effects and collinearity are caveats when interpreting such data. Two studies have previously performed multivariable abandonment assessments, and both excluded patients who refused to begin treatment.[20 30] In a retrospective study from Honduras, where abandonment from initiated ALL treatment (22.8% of 162 patients) was analysed using time-sensitive multivariable regression, travel time >2 hours and low age were associated with less adherence; prognosis and gender were unrelated to adherence; and there was no information on patient socioeconomic status and to what extent patient costs were covered.[20] In a prospective study from a paediatric oncology centre in El Salvador, abandonment from initiated treatment for all cancers (13% of 612) was analysed without accounting for censoring.[30] All direct patient costs for treatment, travel and housing were covered, and yet family income level and numbers of family members were the only

Table 2 Prognostic classification among patients who stated perceived 'poor prognosis' as reason not to adhere to curative cancer treatment

	Prognosis favourable		Prognosis intermediate		Prognosis poor		Total		P value
	n	%	n	%	n	%	n	%	
Not starting treatment									
Due to 'poor prognosis'	12	9.2	22	16.9	96	73.8	130	100	
Other causes for non-adherence	31	28.7	41	38.0	36	33.3	108	100	<0.0001
Not continuing treatment									
Due to 'poor prognosis'	6	37.5	5	31.3	5	31.3	16	100	
Other causes for non-adherence	25	35.7	28	40.0	17	24.3	70	100	0.66

Table 3 Adherence to treatment. *Model 1*: Multivariable logistic regression with OR of starting prescribed curative cancer treatment among patients offered curative treatment for childhood cancer (n=677). *Model 2*: Log-rank test and multivariable Cox regression with HR of not continuing treatment among patients starting treatment (n=438)

	Starting treatment (model 1)				Continuing treatment (model 2)							
Covariates	n	%	OR (CI)	P value	n	1week	1month	1year	2years	Log-rank	HR (95% CI)	P value
Overall	677	64.8%			438	97.1%	90.8%	80.1%	75.0%			
Age												
<6years	479	66.0%			316	96.4%	89.5%	79.2%	71.9%			
≥6years	198	62.1%			123	99.0%	94.4%	82.7%	82.7%	0.06		
Per year			0.98 (0.94 to 1.02)	0.43							0.94 (0.87 to 1.01)	0.08
Gender												
Male gender (ref)	395	64.8%			256	98.2%	94.3%	84.4%	78.1%			
Female gender	282	64.9%	0.98 (0.69 to 1.38)	0.90	183	95.5%	86.1%	74.2%	71.1%	0.03	1.69 (1.05 to 2.73)	0.03
Prognosis												
Favourable (ref)	172	75.0%			129	98.3%	96.5%	78.1%	72.3%			
Moderate (ref)	250	74.8%			187	96.5%	96.5%	83.5%	77.8%			
Poor	255	48.2%	0.51 (0.41 to 0.64)	<0.0001	123	96.6%	91.7%	77.2%	77.2%	0.62	0.95 (0.68 to 1.31)	0.73
Progress over time												
2008	345	59.7%			206	97.8%	91.1%	77.7%	71.6%			
2009	332	70.2%			233	96.3%	90.6%	82.6%	78.5%	0.42		
Per month			1.04 (1.01 to 1.06)	0.002							0.99 (0.95 to 1.02)	0.41
Travel												
Short distance	340	70.6%			240	98.4%	92.2%	82.1%	75.1%			
Long distance	337	59.1%			199	95.6%	89.3%	78.1%	75.2%	0.50		
Per km			0.998 (0.996 to 0.999)	0.004							1.00 (1.00 to 1.00)	0.10
Regional capture rate												
High capture	345	60.6%			209	96.7%	91.5%	81.2%	74.9%			
Low capture	332	69.3%			230	97.3%	90.0%	78.8%	74.9%	0.77		
Per %			3.66 (0.67 to 19.9)	0.13							1.03 (0.09 to 11.8)	0.98

km, kilometre.

factors associated with abandonment. Gender and protocol length were not correlated with adherence, and prognosis and travel distance were not controlled for.[30] The results from these two publications differ from ours, where only female gender seemed to be a risk factor for failure to *continue* treatment, particularly during the first months of treatment.

Previous studies have highlighted somewhat conflicting evidence on univariate associations between abandonment and prognosis,[18 20 32 43–45] travel distance/time,[18 20 30 32 46 47] age,[18 20 30 35 45 48] gender,[20 30 32 35 45 47] cost,[18 20 30 33 36 47 49 50] side effects,[24 32 33 38 40] patient-doctor interaction,[18 24 36] twinning programmes,[12 37] local protocols,[18] socioeconomic status,[18 24 30 32 33 46 48 51] social support networks,[52] traditional medicine,[53] religion[46] and delays in surgical treatment.[54] The array of risk factors and effect measure variability is a natural consequence of treatment abandonment not being a fixed or biology-driven risk factor, but contextual and modifiable. Yet, few studies have previously analysed factors influencing the decision to *start* cancer treatment by controlling for multiple factors simultaneously. We identified that the decision to *start* treatment depended on prognosis, travel distance and quality improvement, when adjusting also for age, gender and regional capture rate.

Our data are limited to the major referral hospital in Northern Vietnam, but it seems as if the capacity of regional hospitals to detect and refer patients with suspected cancer constitutes an important barrier for many children with cancer in Northern Vietnam. Capacity at regional hospitals for basic maintenance treatment and supportive care has been suggested to increase adherence to treatment in other settings,[20 30] and we hypothesised that regional capture rate could reflect such a general regional capacity for paediatric oncology, but found nothing to support its influence on adherence.

Limitations

By not including socioeconomic status variables in our model, we remain ignorant of its influence and may have reduced our explanatory power for analysing other covariates. Income level and number of children per household have previously been shown to independently correlate with event-free childhood cancer survival in developing countries,[24] and in our study almost 20% of parents reported financial reasons for not adhering to treatment. Insurance level was indirectly included in our analysis: healthcare expenditure of children below 6 years is covered by a national health insurance, while children above 6 years are subject to a certain family co-payment, and we found no sign of this threshold being correlated with adherence to treatment.

Another concern relates to the challenges of maintaining and validating a prospective database in a developing country with limited human resources, an over-crowded ward and language barriers. It was particularly difficult to be certain about the point in time when doctors no longer prescribed cancer treatment with the intention of cure (after which non-adherence per definition no longer can occur). Some patients may have been prescribed curative treatment to a point where discontinuation would be a more rational choice. Though generally complying with the end-points indicated in the registry, we did consider 31 terminally ill patients, who declined treatment in their last week of life, as ineligible for non-adherence, and instead recoded them as censored for mortality. There may have been additional terminally ill patients, registered as non-adherence, for which such an early death date remained unknown to us. This represents a grey area between curative and palliative care, where also the most developed countries would struggle with the terminology. Our intention was not to depart from the international definition of abandonment,[25] but to comply with it to the best of our abilities.

Finally, our results on parental motives must be interpreted in the context of a 90.8% response rate among those not starting treatment, and 62.9% among those not continuing treatment. We acknowledge the potential for selection bias, and that in-depth home-visit interviews would have been more informative, reliable and possibly preventive. Such home-visits would also have enabled the measurement of abandonment-related mortality.

Clinical implications

Childhood cancer is fatal without proper treatment,[25 32 33 55] and our findings imply that fatalism and non-adherence to treatment remain a major cause of mortality in childhood cancer in Northern Vietnam. Adherence failure should be explicitly included as an adverse event in reports on event-free-survival,[25 45] and each centre and country must assess and address the setting-specific relative contribution of different abandonment risk factors in their community. Interventions that specifically address adherence to treatment – such as targeting public perception of childhood cancer as a curable condition,[45] tailoring treatment intensity according to local and individual circumstances, strengthening of paediatric oncology capacity at regional hospitals[20 30] and improving transportation services and guest houses – may have substantial effect on clinical outcomes, at relatively low cost. Through such multidisciplinary collaboration, two recent studies indicate that adherence rates at in Vietnam have increased to approximately 85%.[22 56]

If we assume a baseline survival rate of 70% among fully treated children, then treatment success must increase to impossible 100% to match a rise in treatment adherence from current 54.5% to 77.9%. In other words, the clinical impact of non-medical interventions that increase adherence can surpass what is possible to achieve by medical care improvement alone. The same effect would be achieved if we intervened even further upstreams, and improved detection and referral of children with cancer at regional hospitals. Balancing well-measured costs and effectiveness of paediatric oncology is certainly relevant for all countries with limited funds for health, but it is

seems particularly important that resources in low- and middle-income countries are deployed wisely.

Future directions

Non-adherence to lifesaving treatment tends to elicit questions, and we suggest that constructive criticism is redirected from the parents to the particular circumstances under which they are victims. Non-adherence exposes the tragedy of poverty and exemplifies the health effects of non-comprehensive healthcare systems.

Paediatric oncology has long realised the need to differentiate treatments according to needs and risk factors of individual patients, to avoid the dire consequences of over-treatment and under-treatment. This is equally true in developing countries, but here also other risk factors are at play. Very intensive, modern therapy might not be the best option, due to increased risk of treatment related mortality, but also due to decreased adherence.[57] Paediatric oncology can show the way towards strengthening the national healthcare system in low- and middle-income countries – for sustainable diagnostics, referrals and effectiveness of treatment.[1] If built into the national healthcare system, the solutions that work for children with cancer may also be valuable for referral level paediatric care in general, and for children with other non-communicable diseases.

CONCLUSION

Our study prospectively measured adherence to paediatric oncology treatment in the major referral hospital in Northern Vietnam, and quantified motives and risk factors for non-adherence. Almost half of the parents chose to decline curative care (45.5%), either before (35.2%), or during the course of treatment (10.3%). Most parents reported perceived poor prognosis as the main reason for non-adherence, followed by financial constraints, even in instances when prognosis was favourable and financial treatment support was at hand. The odds of starting treatment increased throughout the study-period, and was independently associated with both prognosis and travel distance. The design of the healthcare system and the economic power of the affected families seem to determine the overall prognosis of children with cancer in the low- and middle-income countries. Measures for diagnostic capacity and increasing adherence will have a substantial impact on childhood cancer survival.

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