Paediatric relapsed acute leukaemia: curative intent chemotherapy improves quality of life

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Abstract

Objectives. Paediatric patients with leukaemia with relapse or induction failure have poor prognosis. Anticipated quality of life (QoL) is important in treatment decision making. The objective was to determine if curative intent at relapse or induction failure, when compared with palliative intent, was associated with child's physical health, pain or general fatigue and parents' QoL over time among patients with paediatric leukaemia in El Salvador.

Methods.. This was a prospective observational cohort study. Children 2–18 years with acute leukaemia at first relapse or induction failure were eligible. Assessments occurred every 2 months for up to 2 years using validated proxy report and self-report scales, where guardians were the primary respondents. Initial curative or palliative intent was categorised at enrolment by physicians. The impact of initial intent on QoL was assessed using linear mixed effects models and interaction between QoL and time.

Results. Of the 60 families enrolled, initial treatment intent was curative in 31 (51.7%) and palliative in 29 (48.3%). During the 2-year observation period, 44 children died. Initial curative intent significantly improved child's physical health (estimate=8.4, 95% CI 5.1 to 11.6), pain (estimate=5.4, 95% CI 1.5 to 9.2) and fatigue (estimate=6.6, 95% CI 3.2 to 9.9) compared with palliative intent, but not parents' QoL (estimate=1.0, 95% CI −0.8 to 2.8).

Conclusions. Among paediatric patients with acute leukaemia at relapse or induction failure, initial curative intent treatment plan was associated with better physical health, pain and fatigue when compared with palliative intent. A curative approach may be a reasonable option for patients with acute leukaemia even when prognosis is poor.

Key messages

What was already known?

► Pediatric acute leukemia patients with relapse or induction failure living in low and middle income countries have a poor prognosis.

► Anticipated quality of life is central to therapeutic decision making when the prognosis is poor.

What are the new findings?

► Children treated with initial curative intent at relapse or induction failure had significantly better child physical health, less pain and less fatigue compared to those treated with initial palliative intent treatment plan.

► Parent quality of life was similar between those treated with initial curative vs. initial palliative intent therapy.

What is their significance?

► Initial curative intent therapy was associated with better child quality of life when compared with initial palliative intent therapy for pediatric patients with relapsed or induction failure acute leukemia.
► A curative approach may be a reasonable option for patients with acute leukemia even when the prognosis is poor.

Introduction

Cancer outcomes for children with acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) have improved in high-income countries (HIC), where 80%–90% and 50%–60% are expected to survive without recurrence, respectively.[1]When relapse occurs in this setting, up to 50% of children with ALL and 30% of children with AML can be cured, often with the use of haematopoietic stem cell transplantation or immunotherapies.[2–10] However, in low-income and middle-income countries (LMIC), survival for newly diagnosed and relapsed leukaemia is worse than in HIC.

In El Salvador, an LMIC, the 5-year event-free survival (EFS) was approximately 50% in ALL[11] and 24% in AML.[12] Survival following relapse was evaluated more broadly in a Central American cohort.

Following ALL relapse, the 3-year EFS was 22% and the 3-year overall survival (OS) was 28%. Following AML relapse, the 3-year EFS was 6% and the 3-year OS was 8%. For paediatric patients with cancer with poor prognosis, one of the most important therapeutic decisions is whether the intent of therapy should be curative or palliative.[13] Factors influencing this decision include anticipated quality of life (QoL), length of life remaining, impact on the family and costs.

Even though anticipated QoL is central to therapeutic decision making at the time of relapse, little is known about QoL for paediatric patients following relapse in either the HIC or LMIC setting. In a study conducted in Canada, physical health, pain and fatigue were particularly compromised in children and adolescents with cancer who had poor prognosis.[13] Having a child with cancer is also known

to impact on parents' QoL.[14] Estimates of child's or parents' QoL in those treated with curative versus palliative intent are particularly limited.

Consequently, the objective was to determine if curative intent at relapse or induction failure, when compared with palliative intent, was associated with child's physical health, pain or general fatigue and parents' QoL over time among paediatric patients with leukaemia in El Salvador.

Methods

Design and setting

This was a prospective observational cohort study. The setting was the Benjamin Bloom National Children's Hospital (Hospital Bloom) in San Salvador, El Salvador. Hospital Bloom, the only hospital in El Salvador that admits and treats children with cancer, cares for approximately 200 newly diagnosed children and adolescents with cancer each year. Treatment is provided at no cost to families; accommodation and child care are also offered free of charge to families living a long distance from the hospital to reduce abandonment of therapy. Funding for these programmes is provided by Fundación Ayúdame a Vivir (a local non-governmental organisation), the government and international partnerships.

Eligibility criteria

Children with first relapse or induction failure of ALL or AML were eligible. Those between 2 and 18 years of age at relapse with a guardian who could understand Spanish were included. We excluded children who were severely ill at relapse (to an extent that it would not have been appropriate to approach the family for research as determined by the attending physician) and families who refused any treatment including supportive care.

Procedures

The research coordinator approached eligible families in person to discuss the study. Guardians and children provided written informed consent and assent (if applicable) to participate. To cover transportation costs and food purchases, the family was provided a $10 gift certificate with each completed assessment.

Enrolment had to occur within 1 month of first relapse or induction failure. At enrolment, intent of therapy was obtained from the patient's primary physician and was classified as curative versus palliative. Factors influencing intent of therapy included patient, cancer and relapse features as well as the family's preference. A prespecified algorithm for classification was not used. Guardians completed a baseline demographic survey.

In terms of QoL assessments, guardians were the primary respondents and, if possible, the same guardian reported QoL throughout the study. Children at least 5 years of age at enrolment were also invited to self-report their QoL if they could understand Spanish; their participation was optional. QoL assessments occurred at baseline and then every 2 months (±2 weeks). Assessments continued until withdrawal of consent or death, even in the event of subsequent relapse or abandonment of therapy, for a maximum of 2 years.

Outcomes

The primary QoL domains of interest were paediatric patients' physical health, pain and fatigue and parents' overall QoL. Guardian proxy report and paediatric patient self-report (if applicable) were obtained for three instruments: PedsQL 4.0 Generic Core Scales, PedsQL 3.0 Acute Cancer Module and PedsQL Multidimensional Fatigue Scale. Guardians also completed the PedsQL Family Impact Module on behalf of themselves and their family.

The 23-item PedsQL 4.0 Generic Core Scales reflects four dimensions, namely physical, emotional, social and school functioning. Pae-

diatric patients' physical health was derived from this instrument. The 27-item PedsQL 3.0 Acute Cancer Module assesses the following eight dimensions: pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance and communication.[15] Paediatric patients' pain was derived from this instrument. The 18-item PedsQL Multidimensional Fatigue Scale assesses general, sleep/rest and cognitive fatigue. Paediatric patients' general fatigue was derived using this instrument. All three instruments are reliable and valid in healthy populations and in children with cancer.[15–17] The PedsQL Family Impact Module is a multidimensional parent-report scale that was designed to measure the impact of paediatric chronic health conditions on the parent and the family.[18] It measures parents' self-reported physical, emotional, social and cognitive functioning, communication and worry. It also measures parent-reported family daily activities and relationships. This measure is reliable and valid in families of children with chronic diseases.[18] Parents' overall QoL was derived using this instrument. For all instruments, scores were transformed on a scale ranging from 0 (worst health) to 100 (best health). To derive dimension and summary scores, more than half of the items had to be answered for that dimension. The Spanish version and a 1-month recall period were used.

All questionnaires were administered in person by the research coordinator, although if the family was not seen in clinic proximal to an assessment time point it could be obtained by telephone. Respondents were offered the ability to complete the forms on their own or have them read out loud by the research coordinator. Instruments were completed on paper and not electronically.

Analysis

To compare baseline demographics between the curative intent and palliative intent groups, continuous variables were compared using Wilcoxon rank-sum test, while categorical variables were compared using

Fisher's exact test. In order to determine the impact of intent of therapy at relapse or induction failure on QoL, we fit linear mixed

effects models with random effects for subject and assessment time point, and described the estimate for the interaction term between intent and time point with its 95% CI. To identify potential confounders, we also evaluated the effect of child's age, sex, leukaemia relapse type (ALL relapse vs AML relapse, or induction failure with either ALL or AML), whether any guardian was unemployed, mother with less than high school education, father with less than high school education, family income less than $2000 annually, and whether the palliative care team was consulted at initial relapse or induction failure. These factors were based on previous research[19 20] or clinical judgement.

To evaluate the potential for survivor bias, we also depicted the trajectory of physical health, pain, general fatigue and parents' QoL by initial intent of therapy for individual patients who died. We displayed the time points relative to the date of death (in other words months prior to death) and calculated the mean values by group. All analyses were performed using R Studio V.3.6.1 (The R Foundation for Statistical Computing).

Results

Between January 2015 and May 2017, there were 95 potential participants identified; 60 were eligible and agreed to be enrolled. Figure 1 illustrates the flow diagram of patient identification, selection and reasons for exclusion. Out of 50 children eligible to self-report by age, there were 10 who agreed to self-report.

Among the 60 participating families, one moved to a different country and was lost to follow-up after completing the baseline assessment. An additional 44 children died during the 2-year observation period and thus 15 families completed all 12 assessment time points. Most proxy respondents were mothers (n=53); other respondent types were fathers (n=2), grandparents (n=3), aunt (n=1) and sibling (n=1). In terms of proxy report assessments, there were no missing assessment time points prior to death. For child self-report assessments, there were three children who missed only the fi-

nal assessment prior to death. Thus, the completion rate was 461 of 464 (99.4%) of the total possible number of assessment time points (proxy report and self-report combined).

All enrolled children received chemotherapy. At relapse or induction failure, initial treatment intent was categorised as curative in 31 (51.7%) and palliative in 29 (48.3%) by their attending physician. Online supplemental etable 1 describes the initial chemotherapy treatment plan at study enrolment. Table 1 describes the demographic characteristics of children, guardians and households for the entire cohort and stratified by initial intent of treatment.

The most common diagnosis was ALL relapse (48, 80.0%). The distribution of diagnoses was significantly different by intent of therapy, with more children with ALL relapse having initial curative intent compared with AML relapse or induction failure with ALL or AML (p=0.040). The palliative care team was involved at relapse or induction failure in 39 (65.0%), with no significant difference by intent of therapy (table 1).

Those in the initial curative intent group had significantly longer time from initial diagnosis to enrolment compared with the initial palliative intent group (median 36 months (IQR 23–48) vs 14 months (IQR 4–19), p<0.001). No other baseline feature was significantly associated with initial intent of therapy, including distance to the nearest hospital, distance to Hospital Bloom, or difficulty with and barriers to bringing the child to hospital (table 1). The number of mother respondents was similar in the curative intent group (26, 84%) and the palliative intent group (27, 93%; p=0.416) when comparing proxy respondent type.

Online supplemental etable 2 illustrates the characteristics at death of the 44 patients who died during the 2-year study period after enrolment. Most had palliative care involvement in the preceding 1 month prior to death (35, 79.5%) and almost all received pain medication in the preceding 1 week prior to death (43, 97.7%). Table 2 shows the median guardian proxy-reported generic QoL,

cancer-specific QoL and fatigue, along with the number of participants remaining at baseline, 6 months, 12 months, 18 months and 24 months, while online supplemental etable 3 shows detailed QoL assessments at each time point obtained every 2 months.

Figure 1. *Participant recruitment flow diagram*

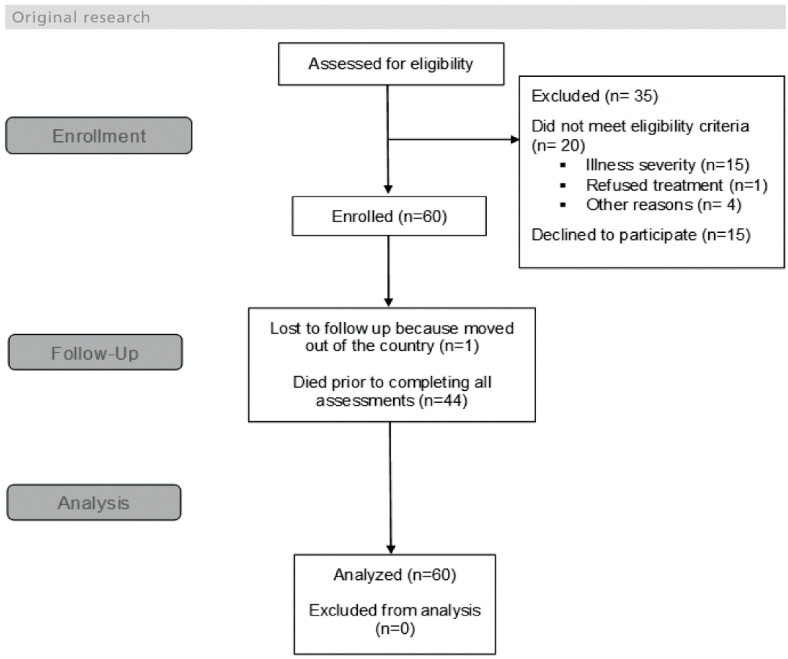


Table 3 shows how the baseline factors impacted change in QoL over time, and figure 2 shows the mean QoL assessments by intent of therapy. Initial curative intent of therapy significantly improved physical health, pain and fatigue over time.

For example, in terms of physical health, those in the curative intent group had on average an 8.4 increase in QoL per month when compared with the palliative intent group (95% CI 5.1 to 11.6). However, initial curative intent did not significantly impact on parent QoL. Table 3 also shows that no other covariate had a significant impact on change in QoL over time.

Online supplemental efigure 1 shows the individual trajectory of physical health, pain, general fatigue and parents' QoL in the curative intent (black line) versus the palliative intent (red line) groups among the 44 children who died. Although QoL was highly variable for individual children, the mean child physical health, pain and fatigue trajectories appeared relatively parallel in the curative intent versus the palliative intent groups.

Discussion

In this prospective observational study of paediatric patients with acute leukaemia at relapse or induction failure in El Salvador, most children died during the 2-year study period. Those treated with initial curative intent at relapse or induction failure, when compared with those treated with initial palliative intent, had significantly better physical health, pain and fatigue over time. This association could not be explained by confounders or survivorship bias.

The association between initial curative intent and better QoL over time was statistically significant even though children treated with palliative intent did not survive beyond 10 months. One possibility is that children treated with a curative intent had better baseline status and better risk disease, thus confounding the association between intent and QoL. However, the graphical display of QoL suggests that baseline QoL was similar in the curative intent and palliative intent groups. A second possibility is that there is survivorship bias, where those with the worst QoL die and are disproportionally removed from the curative and palliative intent groups. However, the individual trajectories of individual patients suggest that QoL in the curative intent group was relatively preserved proximal to death. This finding has important implications since QoL is an important factor clinicians consider when making decisions about treatment in the poor prognosis setting.[13 21]

Table 1. *Demographics of the study cohort (N=60)*

Characteristics	Entire cohort (N=60)	Initial curative intent (n=31)	Initial palliative intent (n=29)	P value†
Child characteristics				
Male, n (%)	40 (67)	19 (61)	21 (72)	0.523
Median age in years at enrolment (range)	8 (3–15)	8 (6–11)	9 (5–12)	0.912
Diagnosis, n (%)				0.040
Relapsed ALL	48 (80)	29 (94)	19 (66)	
Relapsed AML	7 (12)	2 (6)	5 (17)	
Induction failure ALL	1 (27)	0	1 (3)	
Induction failure AML	4 (7)	0	4 (14)	
Initial palliative care at relapse, n (%)	39 (65)	19 (61)	20 (69)	0.725
Median months since initial diagnosis (IQR)	20 (12–37)	36 (23–48)	14 (4–19)	<0.001
Guardian and household characteristics				
Primary caregiver(s)*, n (%)				
Mother	56 (93)	28 (90)	28 (97)	0.654
Father	40 (67)	19 (61)	21 (72)	0.523
Other	12 (20)	8 (26)	4 (14)	0.401
Mother's characteristics, n (%)				
Unemployed	34 (57)	16 (52)	18 (62)	0.578
Education less than high school	28 (47)	12 (39)	16 (55)	0.427
Father's characteristics, n (%)				
Unemployed	6 (10)	2 (7)	4 (14)	0.605
Education less than high school	22 (37)	9 (29)	13 (45)	0.437
Median number of household members (IQR)	5 (4–6)			
Annual household income less than $2000, n (%)	26 (43)	13 (42)	13 (45)	1.000
Access to a phone, n (%)	59 (98)	31 (100)	28 (97)	0.973
Mode of transportation public, n (%)	52 (87)	29 (94)	23 (79)	0.214
Running water at home, n (%)	45 (75)	24 (77)	21 (72)	0.881
Median minutes to nearest hospital (IQR)	40 (29–60)	35 (20–60)	40 (30–60)	0.407
Median minutes to Bloom Hospital (IQR)	120 (85–180)	120 (90–180)	120 (60–180)	0.923

Difficulty bringing child to hospital, n (%)				
Never or rarely	29 (48)	15 (48)	14 (48)	
Sometimes	19 (32)	10 (32)	9 (31)	
Almost always or always	12 (20)	6 (19)	6 (21)	
Barriers to bringing child to hospital, n (%)				
Other children	6 (10)	4 (13)	2 (7)	0.731
Money	38 (63)	21 (68)	17 (59)	0.642
Taking time off work	4 (7)	2 (7)	2 (7)	1.000
Distance to hospital	4 (7)	1 (3)	3 (10)	0.557

*Possible to have more than one primary caregiver type.

†*Continuous* variables compared using Wilcoxon rank-sum test, while categorical variables compared using Fisher's exact test.

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia.

In our study, the median proxy-reported physical health scores were greater than 80 at 10 of 12 follow-up assessment time points. In contrast, the median proxy-reported physical health reported for newly diagnosed children with AML in the Children's Oncology Group (COG) AAML1031 study ranged from 53 to 66 using the same QoL instrument.[22] Similarly, in our study, the median general fatigue scores were 75 or greater at 11 of 12 follow-up assessment time points. In contrast, the median fatigue scores in the COG AML study ranged from 50 to 58. These findings suggest that QoL is higher (better) for patients with leukaemia with relapse or induction failure in El Salvador compared with patients with newly diagnosed AML in North America. This pattern may have occurred because AML treatment is more intensive in North America compared with relapsed leukaemia treatment in El Salvador or because supportive care is better in El Salvador. In terms of the latter possibility, supportive care may be optimised through a twining programme with St Jude Children's Hospital, a palliative and supportive care clinic funded by Fundación Ayúdame a Vivir with governmental aid, or support of nurse educators through the Association of Pediatric Hematology/Oncology Nurses. The other possibility is that perceptions of guardians are different between the two settings.

Table 2 *Guardian proxy-reported quality of life over time (N=60)*

	Baseline	6 months	12months	18 months	24 months
Remaining, n	60	37	22	21	15
Generic Core Scales					
Physical health summary	77 (49–94)	81 (47–97)	88 (73–96)	94 (63–94)	97 (69–100)
Psychosocial summary	70 (57–79)	80 (55–87)	74 (64–87)	78 (58–88)	80 (63–89)
Emotional functioning	58 (44–70)	75 (50–90)	75 (65–89)	80 (65–90)	83 (63–90)
Social functioning	85 (65–95)	80 (60–85)	83 (66–90)	80 (70–100)	95 (64–100)
School functioning	70 (50–80)	75(60–85)	80 (55–75)	65 (65–85)	70 (50–80)
Acute Cancer Module					
Pain and hurt	75 (50–100)	88 (50–100)	100 (88–100)	75 (63–100)	100 (75–100)
Nausea	75 (50–90)	75 (50–90)	80 (53–90)	70 (55–80)	75 (58–83)
Procedural anxiety	50 (17–67)	58 (25–83)	58 (35–90)	58 (42–92)	67 (54–79)
Treatment anxiety	79 (50–100)	92 (58–100)	88 (75–100)	100 (100–100)	100 (75–100)
Worry 75 (48–100)	100 (67–100)	67 (50–96)	67 (50–83)	75 (54–92)	
Cognitive problems	80 (56–94)	75 (60–95)	78 (59–95)	80 (50–88)	88 (75–89)
Perceived physical appearance	75 (50–100)	75 (58–100)	75 (58–100)	83 (50–100)	75 (50–83)
Communication	67 (50–100)	83 (58–100)	79 (50–100)	75 (50–100)	75 (58–92)
Multidimensional Fatigue Scale					
General fatigue	81 (45–92)	75 (50–100)	85 (60–96)	88 (67–100)	92 (71–100)
Sleep/rest fatigue	83 (63–92)	83 (58–100)	94 (72–100)	92 (79–100)	92 (69–100)
Cognitive fatigue	88 (70–100)	83 (58–100)	67 (55–88)	67 (58–79)	75 (60–94)

Data shown as median (IQR) every 6 months.

See online supplemental etable 3 for each assessment. Online supplemental etable 4 shows the median guardian self-reported assessments of parent functioning and family functioning at each time point. Online supplemental etable 5 shows child's self-reported QoL over time.

Table 3. *Factors associated with guardian proxy-reported child quality of life over time**

Variable	Physical health	Pain and hurt	Fatigue	Parent QoL
Initial curative intent (vs initial palliative intent)	8.4 (5.1 to 11.6), p<0.0001	5.4 (1.5 to 9.2), p=0.007	6.6 (3.2 to 9.9), p=0.0002	1.0 (−0.8 to 2.8), p=0.294
Child age in years	0.0 (−0.5 to 0.5), p=0.900	0.1 (−0.3 to 0.5), p=0.606	0.1 (−0.3 to 0.5), p=0.608	−0.1 (−0.2 to 0.1), p=0.508
Male sex	0.3 (−3.2 to 3.8), p=0.877	0.6 (−1.9 to 3.1), p=0.664	−0.5 (−3.4 to 2.4), p=0.743	−0.6 (−1.6 to 0.4), p=0.260
Relapsed acute lymphoblastic leukaemia (vs other)	1.6 (−3.5 to 6.8), p=0.545	−1.6 (−5.5 to 2.3), p=0.429	−1.3 (−5.6 to 3.1), p=0.572	−0.7 (−2.2 to 0.8), p=0.394
Any guardian unemployed	−0.4 (−3.8 to 3.0), p=0.824	−0.4 (−3.0 to 2.2), p=0.769	−0.6 (−3.6 to 2.3), p=0.679	−0.2 (−1.2 to 0.8), p=0.711
Mother with less than high school education	−0.4 (−3.8 to 3.1), p=0.841	0.7 (−1.9 to 3.3), p=0.600	0.2 (−2.7 to 3.2), p=0.894	0.6 (−0.4 to 1.6), p=0.231
Father with less than high school education	−2.4 (−7.3 to 2.5), p=0.359	−1.5 (−5.1 to 2.0), p=0.412	−1.5 (−5.1 to 2.0), p=0.412	−0.1 (−1.1 to 0.9), p=0.891
Family income less than $2000 annually	1.6 (−1.6 to 4.9), p=0.338	2.1 (−0.1 to 4.3), p=0.085	1.5 (−1.3 to 4.3), p=0.303	0.6 (−0.4 to 1.5), p=0.263
Initial palliative care involvement	2.6 (−1.2 to 6.3), p=0.205	1.5 (−1.1 to 4.2), p=0.274	0.2 (−2.8 to 3.3), p=0.881	0.2 (−0.8 to 1.2), p=0.710

**Values* shown are estimate (95% CI) of the interaction between the variable of interest (eg, curative intent) and assessment time point (0–24 months). A statistically significant p value suggests that quality of life is significantly different over time depending on the variable of interest.

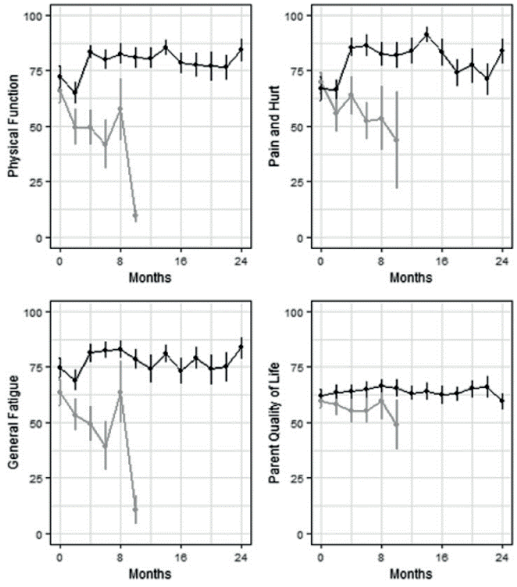
QoL, quality of life.

The strengths of this study include its prospective design among an important and understudied population. The design allowed a unique opportunity to measure the impact of initial curative versus palliative intent of therapy, a comparison which is not amenable to randomisation. The lack of missing data is another important strength, with no missing proxy-report QoL scores among children who died. Consequently, responder bias does not explain our findings. However, this study must also be interpreted in light of its limitation.

The main limitation was the small number of children who self-reported their QoL and consequently the need to rely on proxy report. Another limitation is that we did not evaluate specific chemotherapy medications and their impact on QoL, although this would have been challenging given the number of different chemotherapies, dosages and schedules that would have been used.

In conclusion, among paediatric patients with acute leukaemia at relapse or induction failure, initial curative intent treatment plan was associated with better physical health, pain and fatigue when compared with palliative intent. A curative approach may be a reasonable option for patients with acute leukaemia even when prognosis is poor.

Figure 2. *Child's physical health, pain and general fatigue and parents' quality of life stratified by initial curative intent versus palliative intent at enrolment (N=60). The graph depicts mean proxy-reported physical health, pain and fatigue, and guardian self-reported quality of life. The vertical lines represent the SE. The black line represents those treated with curative intent at enrolment, while the red line represents those treated with palliative intent at enrolment. Enrolment occurred within 1 month of relapse or induction failure*



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