Anaplastic Large Cell Lymphoma in Central America: A Report From the Central American Association of Pediatric Hematology Oncology (AHOPCA)

Francesco Ceppi, MD[1]*; Roberta Ortiz, MD[2]; Federico Antillón, MD[3]; Roberto Vasquez, MD[4]; Wendy Gomez, MD[5]; Jessica Gamboa, MD[6] ; Claudia Garrido, MD[3]; Guillermo Chantada, MD[7,8]; Armando Peña, MD[9]; and Sumit Gupta, MD, PhD[1].

[1]Division of Haematology/Oncology, The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada; [2]Department of Pediatric Oncology, Manuel de Jesus Rivera Hospital, Managua, Nicaragua; [3]National Pediatric Oncology Unit, Francisco Marroquín Medical School, Guatemala City, Guatemala; [4]Department of Onco-Hematology, Hospital Benjamin Bloom, San Salvador, El Salvador; [5]Department of Hematology-Oncology, Dr. Robert Reid Cabral Children's Hospital, Santo Domingo, Dominican Republic; [6]Department of Hematology-Oncology, Hospital Nacional de Niños "Dr.Carlos Saenz Herrera", San José, Costa Rica; [7]Department of Hematooncology, Hospital JP Garrahan, Buenos Aires, Argentina; [8]International Outreach Program, St. Jude Children's Research Hospital, Memphis, Tennessee; [9]Department of Pediatric Hemato-Oncology, Hospital Escuela-Universitario, Tegucigalpa, Honduras

Correspondence to: Francesco Ceppi, Division of Haematology/ Oncology, The Hospital for Sick Children and University of Toronto, 555 University Ave, Toronto, Ontario, Canada M5G 1X8. E-mail: francesco.ceppi@sickkids.ca

 DOI 10.1002/pbc.25698. Published online 8 August 2015 in Wiley Online Library (wileyonlinelibrary.com)

Background. Although anaplastic large cell lymphoma (ALCL) is curable in high-income countries (HIC), data from low- and middle-income countries (LMIC) are lacking. We therefore conducted a retrospective study of the Central American Association of Pediatric Hematology Oncology (AHOPCA) experience in treating ALCL.

Procedure. We included all patients age <18 years newly diagnosed with ALCL treated between 2000 and 2013 in seven AHOPCA institutions. Retrospective data were extracted from the Pediatric Oncology Network Database.

Results. Thirty-one patients met inclusion criteria. Twenty-five (81%) had advanced disease (stages III and IV), six (19%) were treated on the APO (doxorubicin, prednisone, vincristine) regimen, 15 (49%) on multiagent chemotherapy designed for T-cell lineage malignancies (GuatALCL protocol), and 10 (32%) on BFM-based treatment regimens. Five-year overall event-free survival and overall survival were, respectively, 67.1 ± 8.6% and 66.7 ± 8.7%. All 10 events occurred in patients treated on BFM-based treatment regimens or the GuatALCL protocol, none on APO treatment: two patients experienced relapse, six treatment related mortality (TRM), and two abandonment.

Conclusions. Treatment of ALCL in countries with limited resources is feasible with similar outcomes as in HIC, though the causes of treatment failure differ. Less intensive regimens may be preferable in order to decrease TRM and improve outcomes. Prospective clinical trials determining the ideal treatment for LMIC children with ALCL are necessary. Pediatr Blood Cancer. 2016; 63:78–82. ©Wiley Periodicals, Inc.

Introduction

Anaplastic large-cell lymphoma (ALCL), a type of T-cell lymphoma, is a rare disease in children that represents 10–15% of pediatric non-Hodgkin's lymphomas (NHL). [1] First recognized in 1985,[2] its definition has recently been refined by extensive clinical, immunophenotypic, and molecular studies.[3]

There is still no consensus regarding the standard treatment for ALCL. Most European pediatric oncology groups have used shortpulse chemotherapy regimens based on mature B-cell NHL strategies, including high-dose methotrexate (MTX), cyclophosphamide, vincristine, doxorubicin, and corticosteroids with a duration of 4–6 months.[4–8] In North America, patients with ALCL receive prolonged repeated-pulse chemotherapy, with doxorubicin, vincristine, steroids and maintenance with MTX, steroids and 6-mercaptopurine (APO-regimen)[9,10] or in the past with therapy similar to that for T lymphoblastic lymphoma/leukemia (3-week induction therapy followed by a 3-week consolidation period and six courses of maintenance chemotherapy at 7-week intervals).[11] The failure rate at 2 years remains at 30% for most of these regimens.

In 1998, five Central American countries formed the Central American Association of Pediatric Hematology Oncology (AHOPCA), with the goals of investigating disease behavior, developing treatment protocols, and establishing common public health initiatives. [12–14] Initially this consisted of Guatemala, Honduras, El Salvador, Nicaragua, and Costa Rica. Panama joined in 2001 and the Dominican Republic in 2006. In this context it has been possible to design and conduct collaborative studies, and to institute a prospective clinical registry. [13, 15]

Currently, AHOPCA centers use either APO, GuatALCL, or European-based treatment regimens for pediatric ALCL. The last was due in part to international collaboration with several European institutions. [16] Given the different impact of treatment-related mortality in low- and middle-income countries (LMIC) [17, 18] and the lack of any data on ALCL in LMIC, we conducted a retrospective study of the AHOPCA experience in treating ALCL. Our objective was to report the outcomes of ALCL treatment in Central America and the toxicities according to the protocol employed (APO regimen, a compressed aggressive multi-agent Tcell lineage chemotherapy regimen [GuatALCL] vs. European approach).

Method

Study Population and Setting

In this population-based retrospective cohort study, the patient sample consisted of children diagnosed with ALCL and treated in any of the following seven AHOPCA institutions: Benjamin Bloom National Children's Hospital, San Salvador, El Salvador; the National Pediatric Oncology Unit, Guatemala City, Guatemala; Children's Hospital Robert Reid Cabral, Santo Domingo, Dominican Republic; Hospital Nacional de Niños "Dr. Carlos Sáenz Herrera," San José, Costa Rica; Hospital de Manuel de Jesús Rivera "La Mascota," Managua, Nicaragua; Hospital Escuela-Universitario, Tegucigalpa and Hospital Mario Catarino Rivas, San Pedro Sula, Honduras. These sites represent the only pediatric oncology treatment centers in their respective countries.

We included patients aged 0–18 years at diagnosis with de novo ALCL who were diagnosed between January 1, 2000 and December 31, 2013. Immunohistochemical confirmation of diagnosis was attempted using positivity for CD30 and/or ALK protein. CD30 detection was available locally at each center with the exception of Honduras and Nicaragua. When possible, external confirmation of the ALCL diagnosis was obtained through review at the Pathology Department of St. Jude Children's Research Hospital (Memphis, USA).

Cotrimoxazole prophylaxis against pneumocystis pneumonia infection was used for the majority of patients; no other prophylactic was used. Broad-spectrum intravenous antibiotics were started in children with febrile neutropenia. The choice of antibiotics depended on local antimicrobial resistance patterns, available antimicrobials, and cost. All seven centers broadened antibiotics in case of hemodynamic instability and initiated antifungal coverage in patients with prolonged fever. In all seven centers intensive care units with mechanical ventilation and ionotropic support were available. Blood banking practices and availability of blood products varied among centers. El Salvador, Costa Rica, Nicaragua, Dominican Republic,

and Honduras had blood banks available on site, whereas the center in Guatemala was supported by an off-site, private blood bank.

Data Sources

Data were extracted from the Pediatric Oncology Network Database (POND) (www.pond4kids.org). POND is a secure, webbased, multilingual pediatric hematology/oncology database created for use in countries with limited resources to meet various clinical data management needs including cancer registration, delivery of protocol-based care, outcome evaluation, and assessment of psychosocial support programs. [19] Although data collection is primarily to assist in patient outcome monitoring and quality improvement initiatives, data can also be anonymized for research purposes.

In AHOPCA centers, data managers abstract information from patient charts in real time to enter into POND. Treating oncologists confirm data. Routinely collected information includes data on patient demographics, socioeconomic status, diagnosis, treatment, complications, and outcomes. An audit of POND data quality in Honduras showed that accuracy for basic data fields was 99%. [20]

Treatment

Patients with ALCL were treated according to either APO, [9] GuatALCL, [11] or European-based treatment regimens for pediatric ALCL. [4]

The compressed aggressive multi-agent chemotherapy designed for T-cell lineage malignancies; GuatALCL (Supplemental Table I) was based on theCCG-5841 protocol.[11] European-based treatment regimens in use during the study period included the AHOPCA NHL-B protocol, based on the BFM treatment strategy (Supplemental Table II course A-B-A for stages I and II, courses A-B-A-B-A-BA for stage III, and courses AA-BB-AA-BB-AA-BB-AA for stage IV); HD-MTX doses were 1 and 3 g/m2/dose over 3 hr for cycle A and AA, respectively; in cycle A the ifosfamide doses were reduced

to 400 mg/m2/dose from 800mg/m2/dose. Other European based treatments were the AIEOP LNH-97 protocol [21] or NHL BFM-90 protocol. [5] The APO protocol used was based on the standard arm of Pediatric Oncology Group protocol POG-9315 (Supplemental Table III Induction and 15 cycles of maintenance). [9]

Data Variables

Biologic variables included demographic features, such as age and sex, and disease-related features, such as stage, central nervous system status, and bone marrow evaluation. For the calculation of event-free survival (EFS) and overall survival (OS), date of event, date of death, and date of last contact were collected. Cause of death was subdivided into specific causes: infection, bleeding, disease progression, and other causes. The treating clinician determined the cause of death. The determination of events including relapse and progression was left to the local clinical team, as was therefore the need for a biopsy or a specific imaging modality, weighing clinical suspicion, imaging results, and safety. Both ultrasonography and computerized tomography were available in all centers. Abandonment of therapy was defined as 4 weeks of missed appointments during active treatment. Although the length of abandonment considered clinically significant varies between malignancies, a length of 4 weeks has been accepted previously in order to allow comparisons across protocols. [22]

Statistical Methods

OS was defined as the time from diagnosis to death, with patients censored at the time of abandonment. EFS was calculated as the time from diagnosis to first event, with events comprising relapse, death, disease progression, or abandonment of therapy. EFS was also described with patients censored at the time of abandonment. Survival curves were computed using the Kaplan–Meier method. [23] Predictors of EFS and OS were determined using the log-rank test and Cox proportional hazard regression. Of note, given the limited sample size, analyses determining predictors of outcome were considered exploratory and hypothesis-generating only. Statistical analyses were per-

formed using SAS-PC software (version 9.3; SAS Institute, Cary, NC). Statistical significance was defined as P<0.05. The study was approved by the research ethics boards at The Hospital for Sick Children in Toronto, Canada and at each of the Central American sites.

Results

The study sample included 31 children with ALCL treated in the six AHOPCA countries between 2000 and 2013.

Demographic characteristics of the patient population can be seen in Table I. Median age at diagnosis was 9.8 years (interquartile range [IQR] 5.8–13.8 years). Most patients (25, 80.7%) had advanced disease (stages III and IV). Immunhistochemical confirmation of the ALCL diagnosis was obtained in 30/31 (97%) patients. Of the 31 patients, 21 (67.7%) are alive, eight (25.8%) are dead, and two (6.5%) abandoned therapy. Of the 31 patients, six (19.4%) were treated on the APO regimen, 15 (48.4%) on the GuatALCL, and 10 (32.2%) on the European-based treatment regimens (four on the AHOPCA NHL B protocol, four on AIEOP LNH-97, and two on NHL BFM-90).

Table 1. *Patients Characteristics*

No. of patients (N ¼ 31) %		
Gender		
Male	17	54.8
Female	14	45.2
Stage		
II	6	19.4
III	19	61.3
IV	6	19.3
CNS		
Positive	4	12.9
Negative	25	80.6
Unknown	2	6.5
Bone marrow infiltration		
No	27	87.1
Yes	3	9.7
Unknown	1	3.2
Pathology review		
Internal	17	54.8
External	14	45.2
Country		
El Salvador	3	9.7
Nicaragua	4	12.9
Dominican R.	5	16.1
Guatemala	12	38.7
Honduras	3	9.7
Costa Rica	4	12.9
Treatment protocol		
NHL B AHOPCA	4	12.9
GuatALCL	15	48.4
APO	6	19.3
AIEOP LNH-97	4	12.9
NHL BFM-90	2	6.5

CNS, central nervous system; NHL, non-Hodgkin lymphoma; AHOPCA, Central American Association of Pediatric Hematology Oncology; ALCL, anaplastic large cell lymphoma; AIEOP, Pediatric Haemato-Oncology Italian Association; BFM, Berlin-Frankfurt- M€unster.

Considering treatment abandonment as an event, 5-year overall EFS and OS were, respectively, 67.1±8.6% and 66.7±8.7% (Fig. 1). When patients were censored at the moment of treatment abandonment, overall 5-year EFS and OS were 72.7±8.3% and 72.3±8.4%.

The median follow-up was 26 months (IQR 4.8–55.9 months). Five-year EFS (patients censored at abandonment) in patients with localized disease was 100% (n=6) compared to 66.19.9% (n=25) in advanced disease (P=0.13). Five-year EFS (patients censored at abandonment) in patients for whom the pathology was reviewed externally was 83.9±10.5% (n=14) compared to 63.5±12% (n=17) for those only internally reviewed (P=0.19). Of the six patients treated according to the APO regimen, five (83.3%) had advanced stage disease whereas one had Stage 2 disease. The 5-year EFS for these six patients was 100%.

Six events occurred in patients treated on European-based treatment regimens: one patient experienced relapse, four TRM (three infection and one bleeding), and one abandonment. Four events occurred in GuatALCL protocol: three TRM (two infection and one other cause) and one abandonment.

Discussion

We conducted a retrospective study of children with ALCL in six Central American countries treated by the collaborative group AHOPCA. Our results show that the treatment of pediatric ALCL is feasible in LMIC with outcomes equivalent to those in HIC. To our knowledge, this study represents the first report of pediatric ALCL from resource-constrained countries.

Interestingly, the EFS of our Central American population (67.18.6%) does not differ substantially from ALCL cohorts in HIC, the EFS of which have ranged from 71 to 76%.[7,8,10] However, the cause of treatment failure differed significantly. In our population, the main cause of treatment failure was toxicity, unlike in HIC, whe-

re relapses predominate. Increased rates of TRM have been well described in other pediatric malignancies both in Central America and in other LMICs.[17,24–29] As a consequence, and again differently from HIC populations, the EFS of our cohort was very similar to the OS (67.18.6% vs. 66.78.7%).

HIC centers have generally followed one of three ALCL treatment strategies. In one, children with ALCL are treated with BFM-based regimens designed initially for B-cell non-Hodgkin lymphomas.[4] In the second, used mainly in the past, children are treated with compressed aggressive multiagent T-cell lineage chemotherapy regimen, as CCG-5841 protocol.[11] In the third, children are treated with lower intensity chemotherapy cycles but for a longer total duration, as exemplified by the Children's Oncology Group (COG) APO regimen.[10] In HIC centers, these have resulted in equivalent outcomes.[7,10,11] Given the higher burden of TRM, the same may not hold true in LMIC populations. In our study, all events, including all cases of TRM, occurred in children receiving high-intensity BFM-based treatment regimens or intensive GuatALCL protocol. Although we are unable to draw firm conclusions given our small numbers, lower-intensity APO-based regimens warrant further prospective study in LMIC settings. It should be noted that one advantage of BFM-based studies and GuatALCL is their effectiveness in other non-Hodgkin lymphomas. This may be of particular importance in settings where immunohistochemistry and molecular studies for the ALK mutation are unavailable, making it difficult to distinguish ALCL from entities such as diffuse large B-cell lymphomas.

Single agent vinblastine has shown effectiveness in the relapse setting for children with ALCL.[30,31] Although vinblastine holds significant theoretical promise in LMIC, its effectiveness as a front line agent remains unproven,[30,31] and data about toxicity in LMIC populations are lacking. Targeted agents such as brentuximab vedotin, an antibody-drug conjugate combining an anti-CD30 antibody with a potent microtubule inhibitor, and crizotinib, a small molecule inhibitor of the ALK tyrosine kinase, appear to be very promising in

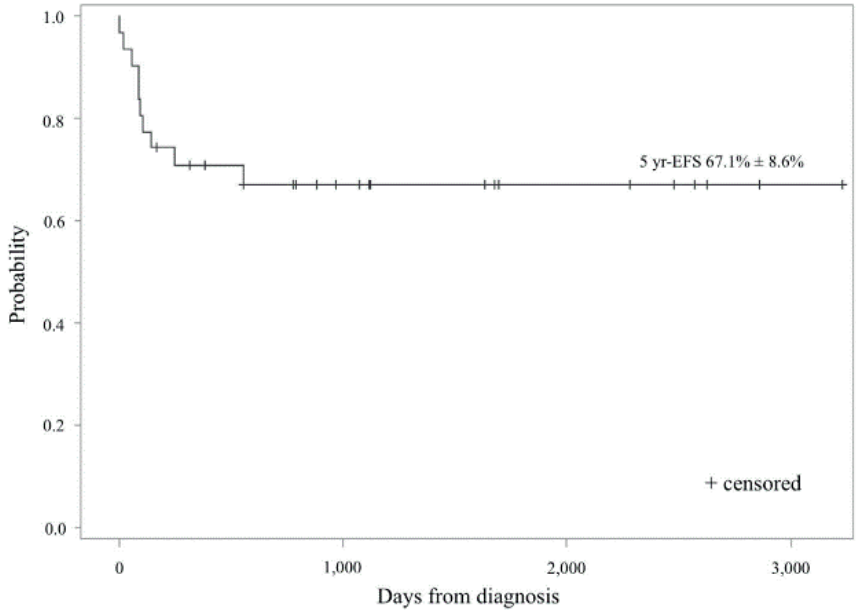
terms of efficacy and safety;[32–34] but their employment in LMICs is limited by availability and cost.

Indeed, our results confirm the need for setting-specific treatment strategies that take into account local realities. Such strategies are likely to differ between HIC and LMIC, and may in fact vary among LMIC. Our results also support international collaborative efforts like those of the International Society of Paediatric Oncology (with the committee Paediatric Oncology in Developing Countries) to create setting-adapted clinical treatment guidelines for the management of children with cancer.[35–39] Our results also illustrate the importance of accurate data and outcomemonitoring of both overall outcomes and cause of treatment failure in order to inform such efforts.

Three main study limitations merit mention. First, the rarity of ALCLresulted in asmall number of eligible patients, even over seven centers and 13 years. We therefore lacked sufficient power to draw definitive conclusions regarding risk factors within our cohort, including the impact of treatment protocol. Second, certain centers used European-based treatment strategies or GuatALCL whereas others used APO-based regimens. We therefore cannot rule out a confounding effect of treatment center when comparing treatment protocols. Third, our study suffers from the limitations inherent to all retrospective cohort studies, where some clinically important details may be unavailable. Despite these limitations, our study represents the first population-based investigation of LMIC pediatric ALCL. Our results can therefore be used as a basis for the design and implementation of prospective trials in this population.

In summary, the treatment of ALCL in countries with limited resources is feasible with similar outcome as HIC. Less intensive regimens, such as APO-based treatment, may be preferable to more intensive chemotherapy regimens given high rates of TRM in LMIC, particularly in settings with access to accurate and timely diagnostic capabilities. Prospective clinical trials are necessary in LMIC to improve the outcome of children with ALCL and validate our results.

Figure 1. *Event-free survival (EFS) with abandonment considered as an event*



References

1. Wright D, McKeever P, Carter R. Childhood non-Hodgkin lymphomas in the United Kingdom: Findings from the UK Children's Cancer Study Group. J Clin Pathol 1997; 50:128–134.

2. Stein H, Mason DY, Gerdes J, O'Connor N,Wainscoat J, Pallesen G, Gatter K, Falini B, Delsol G, Lemke H, Schwarting R, Lennert K. The expression of the hodgkin's disease associated antigen ki-1 in reactive and neoplastic lymphoid tissue: Evidence that reed-sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood 1985; 66:848–858.

3. Damm-Welk C, KlapperW, Oschlies I, Gesk S, Rottgers S, Bradtke J, Siebert R, Reiter A,WoessmannW. Distribution of npm1-alk and x-alk fusion transcripts in paediatric anaplastic large cell lymphoma: A molecular-histological correlation. Br J Haematol 2009; 146:306–309.

4. Reiter A, Schrappe M, Tiemann M, Parwaresch R, Zimmermann M, Yakisan E, Dopfer R, Bucsky P, Mann G, Gadner H, Riehm H. Successful treatment strategy for ki-1 anaplastic large-cell lymphoma of childhood: A prospective analysis of 62 patients enrolled in three consecutive berlin-frankfurt-munster group studies. J Clin Oncol 1994; 12:899–908.

5. Seidemann K, Tiemann M, Schrappe M, Yakisan E, Simonitsch I, Janka-Schaub G, Dorffel W, Zimmermann M, Mann G, Gadner H, Parwaresch R, Riehm H, Reiter A. Short-pulse b-non-hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: A report of the berlin-frankfurt-munster group trial nhl-bfm 90. Blood 2001; 97:3699–3706.

6. Williams DM, Hobson R, Imeson J, Gerrard M, McCarthy K, Pinkerton CR. Anaplastic large cell lymphoma in childhood:

Analysis of 72 patients treated on the united kingdom children's cancer study group chemotherapy regimens. Br J Haematol 2002; 117:812–820.

7. Brugieres L, Le Deley MC, Rosolen A,Williams D, Horibe K, Wrobel G, Mann G, Zsiros J, Uyttebroeck A, Marky I, Lamant L, Reiter A. Impact of the methotrexate administration dose on the need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: Results of a randomized trial of the eicnhl group. J Clin Oncol 2009; 27:897–903.

8. Le Deley MC, Rosolen A, Williams DM, Horibe K, Wrobel G, Attarbaschi A, Zsiros J, Uyttebroeck A, Marky IM, Lamant L,WoessmannW, Pillon M, Hobson R, Mauguen A, Reiter A, Brugieres L.Vinblastine in children and adolescents with high-risk anaplastic large-cell lymphoma: Results of the randomized alcl99-vinblastine trial. J Clin Oncol 2010; 28:3987–3993.

9. Laver JH, Kraveka JM, Hutchison RE, Chang M, Kepner J, Schwenn M, Tarbell N, Desai S,Weitzman S, Weinstein HJ, Murphy SB. Advanced-stage large-cell lymphoma in children and adolescents: Results of a randomized trial incorporating intermediate-dose methotrexate and high-dose cytarabine in the maintenance phase of the APO regimen: A pediatric oncology group phase iii trial. J Clin Oncol 2005; 23:541–547.

10. Alexander S, Kraveka JM,Weitzman S, Lowe E, Smith L, Lynch JC, Chang M, Kinney MC, Perkins SL, Laver J, Gross TG, Weinstein H. Advanced stage anaplastic large cell lymphoma in children and adolescents: Results of anhl0131 a randomized phase iii trial of APO versus a modified regimen with vinblastine: A report from the children's oncology group. Pediatr Blood Cancer 2014; 61:2236–2242.

11. Lowe EJ, Sposto R, Perkins SL, Gross TG, Finlay J, Zwick DA, Bromowitch M. Intensive chemotherapy for systemic anaplastic large cell lymphoma in children and adolescents: Final results of

children's cancer group study 5941. Pediatr Blood Cancer 2009; 52:335–339.

12. Barr RD, Antillon Klussmann F, Baez F, Bonilla M, Moreno B, Navarrete M, Nieves R, Pena A, Conter V, De Alarcon P, Howard SC, Ribeiro RC, Rodriguez-Galindo C, Valsecchi MG, Biondi A, Velez G, Tognoni G, Cavalli F, Masera G. Asociacion de hemato-oncologia pediatrica de centro america (ahopca): A model for sustainable development in pediatric oncology. Pediatr Blood Cancer 2014; 61:345–354.

13. Antillon F, Baez FL, Barr R, Barrantes Zamorra JC, Carrasco LF, Moreno B, Bonilla MM, Tognoni G, Valsecch MG, Howard S, Ribeiro RC, Masera G. Amor: A proposed cooperative effort to improve outcomes of childhood cancer in central america. Pediatr Blood Cancer 2005; 45:107–110.

14. Masera G, Baez F, Biondi A, Cavalli F, Conter V, Flores A, Fontana G, Fossati Bellani F, Lanfranco P, Malta A, Mendez G, Ocampo E, Pacheco C, Riva L, Sala A, Silva F, Sessa C, Tognoni G. North-south twinning in paediatric haemato-oncology: The la mascota programme, nicaragua. Lancet 1998; 352:1923–1926.

15. Wilimas JA, Ribeiro RC. Pediatric hematology-oncology outreach for developing countries. Hematol Oncol Clin North Am 2001; 15:775–787.

16. Howard SC, Marinoni M, Castillo L, Bonilla M, Tognoni G, Luna-Fineman S, Antillon F, Valsecchi MG, Pui CH, Ribeiro RC, Sala A, Barr RD, Masera G. Improving outcomes for children with cancer in lowincome countries in latin america: A report on the recent meetings of the monza international school of pediatric hematology/oncology (mispho)-part i. Pediatr Blood Cancer 2007; 48:364–369.

17. Gupta S, Antillon FA, Bonilla M, Fu L, Howard SC, Ribeiro RC, Sung L. Treatment-related mortality in children with acu-

te lymphoblastic leukemia in central america. Cancer 2011; 117:4788–4795.

18. Gupta S, Bonilla M, Fuentes SL, Caniza M, Howard SC, Barr R, Greenberg ML, Ribeiro R, Sung L. Incidence and predictors of treatment-related mortality in paediatric acute leukaemia in el salvador. Br J Cancer 2009; 100:1026–1031.

19. Quintana Y, Patel AN, Arreola M, Antillon FG, Ribeiro RC, Howard SC. Pond4kids: A global web-based database for pediatric hematology and oncology outcome evaluation and collaboration. Stud Health Technol Inform 2013; 183:251–256.

20. Ayoub L, Fu L, Pena A, Sierra JM, Dominguez PC, Pui CH, Quintana Y, Rodriguez A, Barr RD, Ribeiro RC, Metzger ML,Wilimas JA, Howard SC. Implementation of a data management program in a pediatric cancer unit in a low income country. Pediatr Blood Cancer 2007; 49:23–27.

21. Pillon M, Gregucci F, Lombardi A, Santoro N, Piglione M, Sala A, D'Amore ES, De Santis R, Casale F, Zecca M, Mussolin L, Rosolen A. Results of aieop lnh-97 protocol for the treatment of anaplastic large cell lymphoma of childhood. Pediatr Blood Cancer 2012; 59:828–833.

22. Mostert S, Arora RS, Arreola M, Bagai P, Friedrich P, Gupta S, Kaur G, Koodiyedath B, Kulkarni K, Lam CG, Luna-Fineman S, Pizer B, Rivas S, Rossell N, Sitaresmi MN, Tsimicalis A, Weaver M, Ribeiro RC. Abandonment of treatment for childhood cancer: Position statement of a siop podc working group. Lancet Oncol 2011; 12:719–720.

23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:451–481.

24. Navarrete M, Rossi E, Brivio E, Carrillo JM, Bonilla M, Vasquez R, Pena A, Fu L, Martinez R, Espinoza CM, Lacayo LF, Ro-

driguez H, Batista R, Barr R, Howard SC, Ribeiro RC, Masera G, Biondi A, Conter V, Valsecchi MG. Treatment of childhood acute lymphoblastic leukemia in central america: A lower-middle income countries experience. Pediatr Blood Cancer 2014; 61:803–809.

25. Metzger ML, Howard SC, Fu LC, Pena A, Stefan R, Hancock ML, Zhang Z, Pui CH, Wilimas J, Ribeiro RC. Outcome of childhood acute lymphoblastic leukaemia in resource-poor countries. Lancet 2003; 362:706–708.

26. Paintsil V, David H, Kambugu J, Renner L, Kouya F, Eden T, Hesseling P, Molyneux E, Israels T. The collaborative wilms tumour africa project; baseline evaluation of wilms tumour treatment and outcome in eight institutes in sub-saharan africa. Eur J Cancer 2015; 51:84–91.

27. Orem J, Mulumba Y, Algeri S, Bellocco R, Mangen FW, Mbidde EK, Weiderpass E. Clinical characteristics, treatment and outcome of childhood burkitt's lymphoma at the uganda cancer institute. Trans R Soc Trop Med Hyg 2011; 105:717–726.

28. Widjajanto PH, Sumadiono S, Purwanto I, Sutaryo S, Veerman AJ. L-asparaginase: Long-term results of a randomized trial of the effect of additional 3 doses during consolidation treatment in the indonesian wkall- 2000 protocol. J Pediatr Hematol Oncol 2013; 35:597–602.

29. Yadav SP, Rastogi N, Kharya G, Misra R, Ramzan M, Katewa S, Dua V, Bhat S, Kellie SJ, Howard SC. Barriers to cure for children with cancer in india and strategies to improve outcomes:Areport by the indian pediatric hematology oncology group. Pediatr Hematol Oncol 2014; 31:217–224.

30. Brugieres L, Pacquement H, Le Deley MC, Leverger G, Lutz P, Paillard C, Baruchel A, Frappaz D, Nelken B, Lamant L, Patte C. Single-drug vinblastine as salvage treatment for refractory or re-

lapsed anaplastic large-cell lymphoma: A report from the french society of pediatric oncology. J Clin Oncol 2009; 27:5056–5061.

31. Garner R, Li Y, Gray B, Zori R, Braylan R, Wall J, Hunger SP. Long-term disease control of refractory anaplastic large cell lymphoma with vinblastine. J Pediatr Hematol Oncol 2009; 31:145–147.

32. Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, Matous J, Ramchandren R, Fanale M, Connors JM, Yang Y, Sievers EL, Kennedy DA, Shustov A. Brentuximab vedotin (sgn-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: Results of a phase ii study. J Clin Oncol 2012; 30:2190–2196.

33. Gambacorti-Passerini C, Messa C, Pogliani EM. Crizotinib in anaplastic large-cell lymphoma. N Engl J Med 2011; 364:775–776.

34. Mosse YP, Lim MS, Voss SD, Wilner K, Ruffner K, Laliberte J, Rolland D, Balis FM, Maris JM, Weigel BJ, Ingle AM, Ahern C, Adamson PC, Blaney SM. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: A children's oncology group phase 1 consortium study. Lancet Oncol 2013; 14:472–480.

35. Hesseling P, Israels T, Harif M, Chantada G, Molyneux E. Practical recommendations for the management of children with endemic burkitt lymphoma (bl) in a resource limited setting. Pediatr Blood Cancer 2013; 60:357–362.

36. Israels T, Renner L, Hendricks M, Hesseling P, Howard S, Molyneux E. Siop podc: Recommendations for supportive care of children with cancer in a low-income setting. Pediatr Blood Cancer 2013; 60:899–904.

37. Israels T, Moreira C, Scanlan T, Molyneux L, Kampondeni S, Hesseling P, Heij H, Borgstein E, Vujanic G, Pritchard-Jones K,

Hadley L. Siop podc: Clinical guidelines for the management of children with wilms tumour in a low income setting. Pediatr Blood Cancer 2013; 60:5–11.

38. Chantada G, Luna-Fineman S, Sitorus RS, Kruger M, Israels T, Leal-Leal C, Bakhshi S, Qaddoumi I, Abramson DH, Doz F. Siop-podc recommendations for graduated-intensity treatment of retinoblastoma in developing countries. Pediatr Blood Cancer 2013; 60:719–727.

39. Parkes J, Hendricks M, Ssenyonga P, Mugamba J, Molyneux E, Schouten-van Meeteren A, Qaddoumi I, Fieggen G, Luna-Fineman S, Howard S, Mitra D, Bouffet E, Davidson A, Bailey S. Siop podc adapted treatment recommendations for standard-risk medulloblastoma in low and middle income settings. Pediatr Blood Cancer 2015; 62:553–564.