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Paediatric non-Hodgkin lymphoma in low and middle income countries

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Summary

Great advances have been made in the treatment of paediatric non-Hodgkin lymphoma (NHL). In high-income countries (HIC), cure rates now exceed 85%. However, in low- and middle-income countries (LMIC), cure rates remain less than 50%. It is estimated that over 90% of paediatric NHL worldwide occur in LMIC; therefore, even modest improvements in outcome would have significant impact in reducing the burden of paediatric NHL globally. This article will discuss some of the issues required to improve the outcome of paediatric NHL in LMIC using data presented at the *Fifth International Symposium on Childhood, Adolescent and Young Adult Non-Hodgkin Lymphoma held in Varese, Italy, 2015* to illustrate these issues. Additionally, potential bi-directional benefits for patients in both LMIC and HIC from future collaborations will be discussed.

Keywords

Paediatric; non-Hodgkin lymphoma; developing countries

Scope of the Problem

The incidence of non-Hodgkin lymphoma (NHL) in children younger than 20 years in the United States (US) is approximately 10 cases per million, accounting for approximately 7% of all paediatric cancers (Ries, *et al* 1999). Burkitt lymphoma (BL) is the most common paediatric NHL in the US (40% of patients), followed by lymphoblastic lymphoma (25%), diffuse large B-cell lymphoma (10%) and anaplastic large cell lymphoma (10%) (Ries, *et al* 1999). The incidence of paediatric NHL globally is not accurately known. However, the incidence of NHL in children appears to be dramatically higher in many parts of the world, e.g. in sub-Saharan Africa, where the incidence of BL is 10- to 20-fold higher than in the US (Aka, *et al* 2012), and in regions of Guatemala, where malaria is endemic, a 2- to 4-fold higher incidence of BL is observed (Garrido, *et al* 2015). Over 80% of paediatric cancers

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globally occur in children who live in low and middle income countries (LMIC), (Rodriguez-Galindo, *et al* 2015); therefore, it is estimated that 90% of children diagnosed with NHL live in LMIC.

Between 1975 and 2010, the 5-year survival rate for paediatric NHL in the US has increased, from 45% to 87% in children younger than 15 years and from 48% to 82% for adolescents aged 15 to 19 years (Smith, *et al* 2014). This improvement is largely attributed to the ability to give intensive chemotherapy regimens utilizing high doses of alkylating agents (cyclophosphamide or ifosfamide) and antimetabolites (methotrexate and cytarabine) in combination with other agents (Cairoet al 2007, Patte et al 2007, Woessmann et al 2005). However, in LMIC, survival of paediatric NHL ranges from less than 30% to over 70%, depending on the capacity to support patients through the more intensive regimens (Asirwa, *et al* 2015, Vilas Boas, *et al* 2015, Bouda, *et al* 2015, El-Kababri, *et al* 2015, Garrido, *et al* 2015, Geriga, *et al* 2015, Mutai, *et al* 2015, Otieno, *et al* 2015, Stanley, *et al* 2015, Yalcin, *et al* 2015).

BL is the most common paediatric NHL globally. Given that more data exist for BL in LMIC, the rest of this article will focus on the issues and challenges for improving outcome of BL in children around the world, though the issues are pertinent to all types of paediatric NHL and most paediatric cancers.

Diagnosis and staging

Pathological confirmation of disease is not uniformly performed in LMIC. This is due to a variety of reasons: 1) anatomic location and lack of surgical capacity to safely obtain a tissue diagnosis, 2) poor clinical status of patient at presentation, 3) lack of pathology capacity, including tissue processing, staining, etc., and 4) inability to afford diagnostic procedures. Lack of immunohistochemistry (IHC) is common even when tissue diagnosis is made. A report from Uganda demonstrated that, in cases with a tissue diagnosis of BL, upon US pathological review with IHC, 30% of diagnoses were determined not to be BL (Geriga, *et al* 2015). Lymphoblastic lymphoma was the most common confirmed diagnosis (25%) followed by retinoblastoma (8%), rhabdomyosarcoma (6%), Ewing tumour (6%) and cancer was ruled out in 4% of cases (personal communication F. Geriga, Uganda Cancer Institute, Kampala, Uganda and C. Casper, Fred Hutchinson Cancer Research Center, Seattle, WA, USA). Though most of these tumours would probably respond to commonly used cyclophosphamide-based regimens, they are unlikely to be cured. Given that many paediatric tumours are “small round blue cell tumours”, determining the minimum criteria necessary to make an accurate diagnosis is required to accurately define results of any treatment of BL.

As in high-income countries (HIC), the Murphy staging system is most often used in LMIC (Murphy *et al* 1989). However, in most places in the world, staging consists of clinical examination, chest X-ray and perhaps abdominal ultrasound, along with evaluation of the bone marrow and cerebrospinal fluid (CSF), though cytospin is not always part of CSF evaluation. However, due to the poor clinical condition of a patient at presentation, unavailability of diagnostic equipment or lack of experienced personnel in interpretation of bone marrow and/or CSF evaluation, complete staging may not occur. This is illustrated in a

report from Kenya, where up to 25% of patients did not have full staging performed (Asirwa, *et al* 2015). In HIC, accurate staging is essential for treatment assignment, i.e. presence of surgically resected disease (good risk) and requiring relatively minimal therapy, but marrow and/or central nervous system involvement (poor risk) requires very intensive therapy. However, treatment stratification is not pertinent in most LMIC. Presentation with limited disease is not common and surgical access and capacity is limited. In addition, the capacity to intensify therapy for poor risk disease is very limited for high-risk patients. Therefore, until the capacity to administer more intensive regimens is gained, improving the capability for more comprehensive staging will have a little significant effect on the improving outcome of paediatric NHL in LMIC. However, consensus in staging criteria and reporting are essential for the comparison of results across studies or centres.

Treatment

Access to radiation therapy and oncological surgery expertise is rare in LMIC. However, radiation therapy and surgery have not been shown to have a significant role in the treatment and cure of BL (Sandlund, *et al* 1996, Cairo, *et al* 2007, Patte, *et al* 2007, Woessmann, *et al* 2005). In 1970, an approximately 50% cure rate of stage I-III patients with single agent cyclophosphamide (1.2 g/m^2) was demonstrated for paediatric BL in Uganda (Ziegler, *et al* 1970). Even with limited resources, cure rates of 70-80% can be achieved using similar regimens in patients with limited disease, i.e. stage I-II. However, due to the common presentation with co-morbidities and lack of capacity to deliver sufficient supportive care for the administration of more intensive chemotherapy regimens, the outcome for more advance disease remains a significant challenge in LMIC (Asirwa, *et al* 2015, Vilas Boas, *et al* 2015, El-Kababri, *et al* 2015, (Garrido, *et al* 2015, Geriga, *et al* 2015, Otieno, *et al* 2015, Stanley, *et al* 2015).

Patients presenting co-morbidities at diagnosis is common in patients in LMIC. Patients often present with active infection(s), e.g. malaria or other parasitaemia. Due to late presentation, tumour lysis syndrome can be present at diagnosis, but dialysis or urate oxidate is rarely available, making it a challenge to even treat many patients. Additionally, many patients present with significant malnutrition, which has been associated with inferior outcome (Geriga, *et al* 2015, Otieno, *et al* 2015, Stanley, *et al* 2015). A good example of a low-cost intervention to improve nutrition and hydration comes from Kenya where placement of nasogastric feeding tubes is routine practice. This allows for additional protein-rich feeding and assures hydration, resulting in better tolerance of chemotherapy (personal communication FC Aswira, F Njuguna, [Moi Teaching and Referral Hospital, Eldoret, Kenya]).

Some LMIC centres have been able to improve supportive care and deliver more intensive therapy. In Guatemala, methotrexate (1 g/m^2) has been incorporated into the chemotherapy for BL and an overall survival of 83% has been achieved, though outcome for stage IV patients remains poor (Garrido, *et al* 2015). The French-African Paediatric Oncology Group (GFAOP) in North Africa has used Lymphome Malin B (LMB) therapy, i.e. methotrexate (3 g/m^2) for Group B patients (unresected stage I-III and marrow disease ≤25% involvement) or methotrexate (8 g/m^2) for Group C (marrow involvement >25% or central nervous system

disease). From 2005-08, survival for stage III patients was 68%, but increased to 80% between 2008 and 2014. This improvement could not be attributed to a change in therapy, but demonstrated the value of experience and familiarity with delivery of the therapy and providing improved supportive care. However, survival for stage IV patients still remains poor, at 30% (El-Kababri, *et al* 2015). In sub-Saharan Africa, the GFAOP, using a modified LMB regimen including methotrexate (3 g/m^2), showed 61% survival in stage III patients, though toxic death (9%) remains problematic in these countries (Bouda, *et al* 2015).

Not all efforts to intense therapy have resulted in improved outcome. In Malawi, intensification of therapy in more advanced disease by the addition of doxorubicin through the administration of the CHOP (cyclophosphamide, hydroxy-doxorubicin, vincristine, prednisone) regimen was attempted (Stanley, *et al* 2015). They observed more problems with toxicity and disease control was not improved; therefore, they were unable to demonstrated improvement compared to historical controls without the addition of doxorubicin.

Another significant barrier to improving the outcome of BL in LMIC is the inability to complete therapy, i.e. abandonment (Asirwa, *et al* 2015, Bouda, *et al* 2015). However, in Guatemala, they were able to reduce abandonment through interventions to provide more socioeconomic support and this has contributed to improved survival rates (Garrido, *et al* 2015).

Potential Bi-Directional Benefit

Efforts to standardize minimal criteria for diagnosis and staging, provision of socioeconomic support to reduce abandonment of therapy, improving supportive care (including nutritional support) and implementation of standard treatment protocols, so that health care teams can become experienced and provide better supportive care for patients, are steps that have been demonstrated to improve outcome and have been successfully implemented in even the most resource-challenged settings (Asirwa, *et al* 2015, Bouda, *et al* 2015, El-Kababri, *et al* 2015, Garrido, *et al* 2015, Geriga, *et al* 2015, Otieno, *et al* 2015, Stanley, *et al* 2015). It is evident that support and advice from HIC countries, e.g. GFAOP in North and sub-Saharan Africa, can have great benefits (Bouda, *et al* 2015, El-Kababri, *et al* 2015). The value of having the opportunity for our colleagues in LMIC to share experiences and learn from each other should not be overlooked (Rodriguez-Galindo, *et al* 2015). A great example of this is the Central America Association of Paediatric Haematology and Oncology (AHOPCA) (Garrido, *et al* 2015).

However, there are also opportunities for HIC to gain information and knowledge about the biology and treatment of BL from carefully designed and monitored clinical studies in LMIC. For example, it appears the addition of methotrexate may improve outcome, at least for stage III patients, but the optimal dose without excess toxicity based on healthcare delivery capacity remains to be determined, (Asirwa, *et al* 2015, Bouda, *et al* 2015, El-Kababri, *et al* 2015, Garrido, *et al* 2015, Geriga, *et al* 2015). The experience of the G.F.A.O.P. is very interesting. They administer high-dose methotrexate (3 or 8 g/m^2) using aggressive hydration and folinic acid rescue, but do not follow methotrexate serum levels or

report significant methotrexate-associated toxicities (Bouda, *et al* 2015, El-Kababri, *et al* 2015).

There also remain many interesting and potentially very important biology questions to be answered in BL that can only be answered in LMIC, for example the role of malaria and Epstein-Barr virus (EBV) in the pathogenesis of “endemic” BL. Another important question, is “endemic” and “sporadic” BL the same disease? Certainly, the proportion of EBV-positive cases and anatomic predilection differ between “endemic” and “sporadic” BL, but the biological mechanisms and potential clinical implications remain unknown. Preliminary studies suggest “endemic” and “sporadic” BL may also differ in their molecular genetics (Schmitz, *et al* 2012). Answers to these questions may have significant implications in defining the optimal therapy for BL in LMIC and, perhaps, in HIC.

It could be very important to know if “endemic” BL is truly the same disease as “sporadic” BL. In HIC, survival for paediatric BL now exceeds 85%; however, it is clear that 50% of patients could be cured with much less toxic and costly therapy. Additionally, the outcome of refractory or recurrent BL is so poor, i.e. <20% even in HIC (Cairo, *et al* 2007), making it ethically difficult to reduce therapy unless we can better identify patients who are curable with less intensive therapies. Therefore, careful study of BL patients in LMIC, who receive less intensive and costly regimens, could potentially identify BL patients in HIC where therapy could be safely reduced.

Conclusions

BL was one of the first cancers cured by chemotherapy alone. In 1970, the outcome for paediatric BL in sub-Saharan Africa was as good as any paediatric cancer in the world. It is a travesty that the outcome for BL in many parts of the world is no better than in 1970, while cures rate now exceed 85% in HIC. With only an estimated 10% of paediatric NHL cases occurring in HIC, if all paediatric NHL patients in HIC were cured, approximately 200 more patients would survive, or 1-2% of patients worldwide. However, with 90% of paediatric NHL occurring in LMIC, with only a 15% increase in survival, approximately 2500 patients would be saved, i.e. more than all the paediatric NHL patients in HIC. Therefore, to significantly reduce the burden of paediatric NHL globally, the greatest return on investment is in LMIC.

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References

Aka P, Kawira E, Masalu N, Emmanuel B, Brubaker G, Magatti J, Mbulaiteye SM. Incidence and trends in Burkitt lymphoma in northern Tanzania from 2000 to 2009. Pediatr Blood Cancer. 2012; 59:1234–1238. [PubMed: 22618958]

Asirwa FC, Njuguna F, Busakhala N. Burkitt lymphoma at a public pediatric referral cancer center in Western Kenya. Br J Haematol. 2015; 171:88. abstract 183.

Bouda C, Traore F, Atteby JJ, Raquin MA, Guedenon KM, Pondy A, Moreira C, Harif M, Patte C. A multicenter study of the Groupe Franco Africain d'Oncologie Pediatrique for the treatment of

children with Burkitt lymphoma in sub-Saharan countries. Br J Haematol. 2015; 171:79. abstract 161.

Cairo MS, Gerrard M, Sposto R, Auperin A, Pinkerton CR, Michon J, Weston C, Perkins SL, Raphael M, McCarthy K, Patte C. for the FAB LMB96 International Study Committee. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood. 2007; 109:2736–2743. [PubMed: 17138821]

El-Kababri M, Cherkaoui S, Hessissen L, Madani A, Khattab M, Quessar A, Barsaoui S, Cherif N, Raquin MA, Raphael M, Patte C, Harif M. Childhood Burkitt lymphoma in North Africa: a study of the French-African Pedatric Oncology Group (G.F.A.O.P.). Br J Haematol. 2015; 171:2. abstract 3.

Garrido C, Giron V, Castellanos M, Valverde P, Letona T, Osorio E, Antillon F. Burkitt's lymphoma at the Unidad Nacional De Oncologia Pediatrica (UNOP) Guatemala. Br J Haematol. 2015; 171:3. abstract 4.

Geriga F, Mutyaba I, Kambugu J, McGoldrick S, Casper C, Orem J. Presentation and treatment outcomes of children with Burkitt lymphoma at Uganda Cancer Institute. Br J Haematol. 2015; 171:43. abstract 75.

Murphy SB, Fairclough DL, Hutchison RE, Berard CW. Non-Hodgkin's lymphomas of childhood: an analysis of the histology, staging, and response to treatment of 338 cases at a single institution. J Clin Oncol. 1989; 7:186–93. [PubMed: 2915234]

Mutai M, Mtete I, Mehta P, Gopal S, Liomba G, Fedoriw Y, Krysiak R, Kazembe P, El-Mallawany NK. Clinical spectrum of lymphoma in children and adolescents in Central Malawi. Br J Haematol. 2015; 171:78. abstract 159.

Otieno JA, Buckle G, Maranda L, Skiles J, Moormann AM. Survival among Kenyan children treated for endemic Burkitt lymphoma between 2003 and 2011: a longitudinal analysis of risk factors. Br J Haematol. 2015; 171:35. abstract 59.

Patte C, Auperin A, Gerrard M, Michon J, Pinkerton R, Sposto R, Weston C, Raphael M, Perkins SL, McCarthy K, Cairo MS. for the FAB LMB96 International Study Committee. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. Blood. 2007; 109:2773–2780. [PubMed: 17132719]

Ries, LAG.; Smith, MA.; Gurney, JG.; Linet, M.; Tamra, T.; Young, JL.; Bunin, GR., editors. Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. National Cancer Institute; Bethesda, MD: 1999. p. 1975-1995.

Rodriguez-Galindo C, Friedrich P, Alcasabas P, Antillon F, Banavali S, Castillo L, Israels T, Jeha S, Harif M, Sullivan MJ, Quah TC, Patte C, Pui CH, Barr R, Gross T. Toward the Cure of All Children With Cancer Through Collaborative Efforts: Pediatric Oncology As a Global Challenge. J Clin Oncol. 2015; 33:3065–3073. [PubMed: 26304881]

Sandlund JT, Downing, JR; Crist, WM. Non-Hodgkin's lymphoma in childhood. N Engl J Med. 1996; 334:1238–48. [PubMed: 8606720]

Schmitz R, Young RM, Ceribelli M, Jhavar S, Xiao W, Zhang M, Wright G, Shaffer AL, Hodson DJ, Buras E, Liu X, Powell J, Yang Y, Xu W, Zhao H, Kohlhammer H, Rosenwald A, Kluin P, Muller-Hermelink HK, Ott G, Gascoyne RD, Connors JM, Rimsza LM, Campo E, Jaffe ES, Delabie J, Smeland EB, Ogwang MD, Reynolds SJ, Fisher RI, Braziel RM, Tubbs RR, Cook JR, Weisenburger DD, Chan WC, Pittaluga S, Wilson W, Waldmann TA, Rowe M, Mbulaiteye SM, Rickinson AB, Staudt LM. Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics. Nature. 2012; 490:116–120. [PubMed: 22885699]

Smith MA, Altekruse SF, Adamson PC, Reaman GH, Seibel NL. Declining childhood and adolescent cancer mortality. Cancer. 2014; 120:2497–2506. [PubMed: 24853691]

Stanley C, Heimlich JB, El-Mallawany NK, Mtete I, Butia M, Kaimila B, Itimu S, Chikasema M, Chimzimu F, Kampani C, Mzumara S, Montgomery ND, Fedoriw Y, Kazembe PND, B M, Krysiak R, Liomba NG, Gopal S. Survival among CHOP-treated children with endemic Burkitt lymphoma (eBL) in Malawi. Br J Haematol. 2015; 171:81. abstract 167.

Vilas Boas M, Melaragno R, Noguchi DT, Valeiro TF, Gorender E, Epelman S. Burkitt lymphoma - evaluation of 40 patients in a low-income area. Br J Haematol. 2015; 171:80. abstract 165.

Woessmann W, Seidemann K, Mann G, Zimmermann M, Burkhardt B, Oschlies I, Ludwig WD, Klingebiel T, Graf N, Gruhn B, Juergens H, Niggli F, Parwaresch R, Gadner H, Riehm H, Schrappe M, Reiter A. for the BFM Group. The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the BFM Group Study NHL-BFM95. Blood. 2005; 105:948–958. [PubMed: 15486066]

Yalcin B, Sen HS, Orhan D, Aydin B, Varan A, Kurucu N, Kutluk T, Buyukpamukcu M, Akyuz C. Precursor B-cell lymphoblastic lymphoma in children: Hacettepe experience. Br J Haematol. 2015; 171:68. abstract 138.

Ziegler JL, Morrow RH Jr, Fass L, Kyalwazi SK, Carbone PP. Treatment of Burkitt's tumor with cyclophosphamide. Cancer. 1970; 26:474–484. [PubMed: 5468593]