CHILDHOOD CANCERS IN LOW- AND MIDDLE-INCOME COUNTRIES: PREVENTION AND POTENTIALLY CURABLE TREATMENT?

PROFESSOR TIM EDEN, EMERITUS PROFESSOR OF PAEDIATRIC AND ADOLESCENT ONCOLOGY, MANCHESTER UNIVERSITY, UK

Survival disparity for childhood cancers world wide must be reduced. Infection related malignancies offer the possibility of both prevention and affordable treatment. Burkitt Lymphoma, the most common tumour seen in sub-Saharan Africa can be reduced by improving malaria control and cured in at least 60% of cases by short course affordable drugs. HIV/AIDS control has reduced Kaposi Sarcoma incidence. Greater collaboration between those working in communicable and noncommunicable diseases would benefit all children.

Incidence and prevalence

Survival for children with cancer has increased considerably from under 20% in 1970 to 75–80% in 2017 in high-income countries (HICs) *(1)*. This has resulted from the ability to reduce delays in diagnosis, more accurately diagnose specific tumours and from progressive improvement in treatment. There are still challenges with some high risk tumours *(2)*. However the biggest challenge is that only 20% of children worldwide are benefitting from this progress. Eighty-percent of young people live in low- and-middle income countries (LMICs) where survival rates are currently only 10% in LICs and 30% in most MICs *(3, 4)* with clearly some geographical variation. Inaccuracies do arise where there are no population-based registers of incidence and even fewer of mortality. It is calculated that worldwide between 80 and 100,000 young people die unnecessarily from cancer each year because of a failure of diagnosis, and no or inadequate treatment. However recent evidence has shown a 13% increase in worldwide incidence of cancer in young people aged 0–14 years between the decade 1981–1990 and 2001–2010 *(5)*. The increase in part does relate to increased rates of earlier and more accurate diagnoses and the ability to treat especially in middle-income countries and the reduction of under 5-year deaths in LMICs. Such a trend occurred in higher income countries from the 1950s onwards as general health improved and there was a reduction of mortality from infectious diseases. There is compelling evidence that this trend will continue to increase year on year, albeit with some changes in tumour types seen, as societies and economies in each country begin to change *(5)*.

The International Agency for Research on Cancer (IARC) have recently reported, using data from high-quality, high ascertainment population-based cancer registries on 385,509 incident cancers of children and young adults (0–19 Years) occurring over 2.64 billion person-years *(5)*. The calculated overall incidence rates for those aged 0–14 are now 141 per million and for those aged 15–19, 185/ million *(5)*. It is estimated that worldwide there are at least 215,000 new cases per year of children aged 0–14 years with cancer and 85,000 in the age range 15–19 years *(5, 6)*. These figures may well be an under-estimate because of a paucity of reliable cancer registration in many LMICS. In twinning partnerships where assistance from established paediatric oncology units in high-income countries have helped the developing hospital to register all cases they see in the country's hospitals, there is evidence that only 25–33% of cases expected, based on International childhood cancer rates, are actually being diagnosed and treated *(7)*.

The challenges

This gross disparity is due to a number of factors *(7, 8, 9, 10, 11)*:

- Missed or late diagnoses due to lack of public and health professional awareness of cancer signs and symptoms.
- Lack of diagnostic capability, resources and trained laboratory and radiological staff.
- Paucity of trained nurses and doctors to treat patients plus failure to retain those trained within LMICs.
- Overall inadequate facilities and resources in hospitals.
- High rates of co-morbidities (e.g malaria, HIV, TB,

diarrhoea and malnutrition).

- Lack of availability, accessibility and affordability of good quality Essential Medicines (all on WHO listing).
- High rates of treatment refusal and subsequent abandonment most frequently due to non-affordability and/or perception of incurability (9, 12, 13, 14).
- Overwhelming other society issues including natural and man-made crises.

Poverty

In most LMICs families have to bear the total or at least some of the cancer cost burden including for medicines *(7, 9, 14, 15, 16, 17, 18)*. Individual family, community and Governmental poverty all hinder the development of health services but worse than that, it fails each child who is ill but could be cured if resources were available. Considerable assistance has helped in at least 50 countries through a variety of twinning projects linking established paediatric cancer centres in HICs and those who are striving to develop such units in LMICs *(7, 9, 11)*. This can only be a short- to medium-term solution and not sustainable in the longer term. Ultimately, each country will need to resolve the challenges and finance the care of all patients but universal health coverage is a long-term project. However right now at least 50% of childhood cancers can be cured using relatively cheap generic drugs provided the malignancy is diagnosed early before there is significant tumour dissemination.

Prevention

Where resources and finances are limited then it is important to determine what is potentially a "good buy" for families, the country and each Government *(18, 19)*. This makes an initial focus on treatment of infection-related cancers worthwhile because they all have a communicable disease connection in situations where considerable financial input to reduce infections has already been invested over the last two decades (20) as a result of a worldwide initiative. In many LMICs this has led to reduction in malaria, diarrhoea, pneumonia, malnutrition and those with HIV/AIDS have had their chance of long-term survival greatly improved by antiretroviral agents. All the actions taken for communicable diseases over the last 15 years are also having an impact on the incidence of some childhood cancers.

Prevention is always better than having to treat any cancer. Endemic Burkitt Lymphoma *(21, 22, 23)* arises in sub-Saharan Africa, from a combination of high prevalence rates of Plasmodium falciparum malaria, which produces a degree of T-cell immunosuppression resulting in B-Cell proliferation within which the omnipresent Epstein-Barr Virus also proliferate. Ninety-five percent of Endemic BL cases have high levels of EBV Antibodies implying that infection with the virus preceded the development of the tumour. The proliferating cells appear to be transformed by the virus during the immunosuppression induced by malaria episodes. Other potential co-factors may include arboviruses, endemic plant promotors and malnutrition *(24)*. EBV loads appear to increase with attacks of malaria *(25)*. BL accounts for more than 50% of childhood cancers in many sub-Saharan African countries with a peak age of 6–8 years which suggests that an early age EBV sero-conversion is associated with the high incidence of BL *(26)*.

Furthermore, there is a reported 15-fold increase of BL in those who have acquired immunodeficiency syndrome (HIV/AIDS) *(27, 28)*. Consequently, there is increasing evidence that where strenuous efforts have been made to reduce the risk of malaria (mosquito nets/clearance of stagnant water, etc) and the increased dispensing of antiretrovirals that the incidence of BL and other HIV-related tumours have decreased in some regions *(29)*. Of course, the production of an effective anti-malaria vaccine would not only reduce incidence of recurrent malaria in children and particularly cerebral malaria with its high mortality rate but it would also reduce incidence of BL.

Kaposi Sarcoma caused by Human Herpes Virus-8 (HHV-8) is also endemic in sub-Saharan Africa *(30)* but it has shown a significant fall in incidence following use of ART and reduction of immunosuppression where both HIV and HHV-8 are endemic *(31)*.

Liver cancer accounts for 9% of cancer deaths worldwide with 85% occurring in LMICs especially in Asia. Hepato-cellular carcinoma is linked to hepatitis B and C infection. Although hepatic tumours are relatively rare in children there is increasing evidence that national infant HBV vaccination programmes might reduce liver tumour cancer incidence in children and in adults later in life. In both Taiwan and Gambia large scale infant HBV vaccination programmes started 20 years ago are now confirming a reduction of liver tumour incidence *(32, 33, 34)*.

Prevention is generally rare in childhood cancer but for Burkitt lymphoma, Kaposi Sarcoma, liver tumours and all HIV associated tumours there is hope of preventing tumour formation, provided measures (control of known infections, and/or vaccinations) are applied nationally and persistently. If there is any break in control of infections the tumour incidence will increase once again. As described elsewhere in this journal universal HPV vaccination for pre-adolescent boys and girls would not only reduce the risk of cervical cancer in adults but also potentially other HPV-related malignancies.

Avoiding delays in diagnosis *(35,36,37)*

If we cannot prevent malignancies it is always preferable

to recognize the signs and symptoms of potential cancers/leukaemia and diagnose them before there has been significant tumour secondary spread. Diagnostic delays necessitate more intensive therapy to control the malignancy, an increase in the economic burden on those paying for treatment (most commonly families in low-income countries) and considerably more anxiety for patients and families *(8, 9)*. BL classically presents with large abdominal masses, periorbital/mandibular/maxillary swelling, with or without bone marrow and CNS disease. The signs and symptoms of BL are very characteristic and should never be mistaken for anything but tumours. Luckily this tumour is highly sensitive to cyclophosphamide, methotrexate and vincristine, some of the oldest known cytotoxic drugs. Survival is at least 50% for all stages except those with bulky abdominal disease and in some but not all studies CNS or bone marrow (BM) involvement. Hence the importance of early recognition and treatment. It is clear that with adequate and appropriate treatment both CNS and BM disease can be controlled.

The use of poster campaigns targeted at healthcare workers in local clinics, schools, and wherever families meet can be effective provided the messages are clear and repetitive *(38)*. There does remain a degree of stigma associated with cancer in many societies so late presentation still happens, hence the need not only for local health workers to be trained to identify cancer signs but also to overcome the perception by many families that cancer is not curable in children. The use of all forms of media to complement such awareness campaigns are crucial for success in education of the population and professionals have also been found to be very useful. Parent groups of children with cancer and those survivors of cancer can assist immensely in such awareness campaigns and reinforce the potential for curability.

Treatment

At least 50% of childhood cancers can be cured using basic protocols designed and proven over the last 3–4 decades in HICs which can be applied in a graduated intensity process depending on what each hospital and country can manage *(39)*. There are a series of such guidance protocols produced by expert teams from the International Society of Paediatric Oncology (SIOP) covering most of the commonest tumours seen worldwide including the critical need for supportive care guidelines *(40, 41, 42, 43, 44)* and baseline standards for nursing care *(45)*.

Burkitt Lymphoma in 90% of cases can be cured using intensive chemotherapy which is not yet tolerable in most LMICs *(46)* but from evidence accrued in Cameroon and Malawi *(47, 41)* a stratified regimen (based on stage and response to induction) using induction with just cyclophosphamide (iv or oral on days 1, 8, 15) and intrathecal methotrexate + hydrocortisone (Days 1, 8, 15) and followed by consolidation based on the risk grouping by one or two more doses of cyclophosphamide for risk groups 1 and 2 respectively. Only advanced stage disease (Risk group 3) received three doses plus the addition of vincristine. In the Cameroon study *(47)* overall survival with this strategy was 61% at 1 year (100% Stage 1, 85% Stage 2, 60% stage 3, but only 27% stage 4) emphasizing the need for early recognition of the tumour. Such therapy is affordable (for low stages at just US$ 50 for the drugs), short in duration and very tolerable. The International Network for Cancer Treatment and Research, INCTR 03-06 protocol, used in four tertiary equatorial African centres increased survival from an historic 10–20% to 67% for those treated with a three drug initial programme using cyclophosphamide, methotrexate, vincristine and intrathecal therapy for those who went into remission and 62% for those who failed to remit or relapsed early treated with a salvage therapy using ifosfamide, etoposide and cytarabine. This study clearly showed the impact for survival of abdominal disease *(48)*.

There are similar guidelines for Kaposi Sarcoma *(42)*, Retinoblastoma (44) and Wilms Tumour *(43)* all of which are potentially curable, using such standard therapy provided they can be afforded in low-income settings.

Cost of treatment

In most low-middle income countries families carry most or at least some of the financial burden of their child's cancer treatment and care *(19)* but there are only a few studies to date specifically looking at these out of pocket costs *(15, 16, 17, 18)*. Islam et al *(15)* identified in the largest childhood cancer centre in Bangladesh that the basic costs to parents of treating their child with acute lymphoblastic leukaemia was US$ 4,445 with a range from US$ 3,234 to US$ 7,672 depending on how many infectious episodes the patient had during treatment (mean of three serious episodes). These sums are considerably lower than reported from those in HICs *(49)* but still not affordable when 84% of the families in the Bangladeshi unit at the time of the study were living on between 71 and 285 US$ per month. The breakdown of costs there showed that 48.6% was for the purchase of essential medicines all of which are on the WHO Essential Medicines Listing reviewed every two years *(50)* and 26% for transport to and from hospital, food and accommodation for parents whilst the child was in hospital. Investigations, blood products and general treatment costs accounted for the remainder. All medical consultations were free and there were no bed fees.

However, affordability of the essential medicines is just one of the challenges facing patients/families and those caring for children with cancer in LMICs especially, but increasingly

in all countries. There is an increasing crisis in accessibility, availability, quality and affordability of WHO recommended essential medicines for children with cancer *(51, 52, 53, 54)*. They are all off patent, generic drugs more commonly now acquired from generic pharmaceutical companies in a variety of countries but most frequently from India and China. There are problems of adequate and consistent world-wide drug production and distribution, very variable importation processes, considerable variation in drug costs and efficacy of products with inadequate quality control *(52, 53, 55, 55)*. There needs to be a collective collaboration worldwide with all stakeholders working to overcome these challenges and to ensure all that children with cancer can get a fair deal and a real chance of survival.

Incidence and mortality data/registration

The IARC report on Incidence of childhood cancer 2001–10 *(5)* was a major exercise and very informative about overall numbers, and variations in incidence and the reason for them between countries and continents and identified a 13% upward trend in incidence worldwide since the report covering 1981–1990. But it also highlighted the need for much more consistent universal population-based cancer registration. Of 532 invited registries just 153, albeit from 62 countries, met quality standards for the entire decade and could be included in the analyses. The standards used were to ensure that all the basic information about each patient and their diagnosis were as accurate as possible. When reviewing the data from an initial 532 registries worldwide the following standards were applied by a rigorous peer-review process. The numbers of cases confirmed by tumour tissue examination by microscope, and classified according to international grouping (ICCC–3),the proportion only identified by death certification, exclusion of tumours with unlikely site and morphology or unlikely age and tumour without tissue , if more than > 0.05% were rare tumours, overall absolute and relative incidences , proportions of cases and incidence by sex, age, tumour type and stability or not over time and consistency of population data. These are stringent standards by necessity but they are what each hospital register would hope to collect. Clearly since only 153 registries did tick all the boxes for the whole decade there is some way to go before all registries can conform.

What all involved in cancer care, health services and Governments need to recognize is that you cannot develop appropriate services for cancer or any diseases if you do not know how many cases there are to be diagnosed and treated. What happened in higher-income countries was that those treating children with cancer and leukaemias started to develop hospital-based registries collecting most of the data required by the IARC study and these did lead to linking up between hospitals regarding such data inevitably leading to national registration. This took some years to create in some countries but development was quicker in some European countries.

One of the greatest challenges is the paucity of trained pathologists in many LMICs. Many of the international twinning programmes assist by providing in the modern era remote telepathology review systems as interim measures before the local services can be developed *(7,9)*.

Conclusions

Childhood cancer is potentially a "best buy" for health planners in each country with higher cure rates than adult cancers, and a relatively more manageable incidence rate. In each country planners and medics/nurses need to carefully monitor and record every case, plus their outcome. They need to raise awareness of cancer signs and symptoms amongst the public and health workers to reduce missed or late diagnoses. They must try to create the essential supportive care resources and facilities before starting to treat patients. Using the concept of graduated intensity treatment appropriate to their setting they can start to use therapy which can give chance of cure and escalate treatment if that is possible in due course. This is how the successes in HICs was obtained over several decades.

Endemic cancers especially Burkitt Lymphoma, Kaposi Sarcoma, HIV-related tumours and Hepatic tumours are highly likely to be reduced by control of malaria, HIV/AIDS, and vaccination respectively. Those working in oncology and communicable diseases need to join forces to recognize and collaborate more actively. ■

Professor Tim Eden is Emeritus Professor of Paediatric and Adolescent Oncology at Manchester University in the UK. His research included development and analysis of clinical trials; cancer epidemiology and aetiology, psycho-social functioning and supportive care. He has published over 300 peer reviewed papers, editorials and chapters. He was President of SIOP (2004–2007). He is founding Medical Trustee of World Child Cancer working to develop twinning partnerships between high-income and low-income countries where cancer is emerging as a major threat to the life of children and trying to reduce the gross disparity in care of children worldwide.

References

1. McGregor LM, Metzger ML, Sanders R, Santana V M. Pediatric cancers in the new millennium: dramatic progress, new challenges. Oncology 2007; 21(7):809-820
2. Pritchard-Jones K, Pieters R, Reaman GH, Hjorth L, Downie P, Calaminus G et al Sustaining innovation and improvement in the treatment of childhood cancer :lessons from high income countries. *The Lancet Oncology* 2013; http//dx.doi.org/10.1016/s1470-2045 (13)70010-x
3. Pritchard-Jones K, Sullivan R. Children with cancer: driving the global agenda. *The Lancet Oncology* 2013; 14(March):189-191
4. Magrath I, Steliarova-Foucher E, Epelman S, Ribeiro R C, Harif M, Li C-K et al, Pediatric cancer in low income and middle–income countries. *The Lancet Oncology* 2013;10.1016. s1470-2045(13)700008-1
5. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. International incidence of childhood cancer,2001-2010: a population –based registry study. *The Lancet Oncology* 2017;April11th: http://dx.doi.org/10.1016/s1470-2045(17)30186-9
6. International Agency for Research on Cancer-International Childhood Cancer Day (2016). "Much remains to be done to fight childhood cancer" IARC Press release number 241-15 February 2016
7. Hopkins J, Burns E, Eden T. International twinning partnerships: An effective method of improving diagnosis, treatment and care for children with cancer in low-middle income-countries. *Journal of Cancer Policy* http://dx.doi.org/10.1016/j.jcpo2013
8. Ribeiro RC, Steliarova-Foucher E, Magrath I, Lemerle J, Eden T, Forget C, et al. Baseline status of paediatric oncology care in ten low-income or middle-income countries receiving "My Child Matters" support: a descriptive study. *The Lancet Oncology* 2008;9(August 8):721-9
9. Ribeiro RC, Pui CH. Saving the children – Improving childhood cancer treatment in developing- countries. *New England Journal of Medicine.* 2005; 352(21):2158-2160
10. Israels T, Ribeiro RC, Molyneux EM. Strategies to improve care for children with cancer in Sub-Saharan Africa. *European Journal of Cancer* 2010; 46(11):1960-1966.
11. Masera G, Baez F, Biondi A, Cavalli F, Conter V, Flores A et al. North–South twinning in Paediatric haematol-oncology: the La Mascota Programme, Nicaragua. *The Lancet* 1998; 352; 1923-26
12. Arora RS, Eden T, Pizer B. The problem of treatment abandonment in children from developing countries with cancer. *Pediatr Blood Cancer* 2007;49:941-6
13. Mostert S, Arora RS, Arreola M, Bagai P, Friedrich P, Gupta S et al. Abandonment of treatment for childhood cancer: a position statement of a SIOP PODC Working Group. *The Lancet Oncology* 2011; 12(August (8):719-720
14. Mostert S, Sitaresami H, Gundy CM, Veerman AJ. Influence of socioeconomic status on childhood acute lymphoblastic leukaemia treatment in Indonesia. *Pediatrics* 2006; 118(6) e1600-e1606
15. Islam A, Akhter A, Eden T. Cost of treatment for children with acute lymphoblastic leukaemia in Bangladesh. *Journal of Cancer Policy* 2015;6 :37-43.
16. Liu Y, Chen J, Tang J, Ni S, Xue H, Pan C. Cost of childhood acute lymphoblastic leukaemia care in Shanghai, China. *Pediatric Blood and Cancer* 2009;53(4)557-562
17. Ji X, Xuan Y, Li J, Zhao J, Lu S, Zhang J, Zhao P. Direct costs for Retinoblastoma treatment during the first year of comprehensive therapy in China. *Journal of Paediatric Ophthalmology and Strabismus.* 2012; 49(6), 353-358
18. Ghatak N, Trehan A, Bansal D. Financial burden of therapy in families with a child with acute lymphoblastic leukaemia: report from North India. *Supportive Care in Cancer* 2016; 24(1) 103-108
19. Sullivan R, Kowalczyk JR, Agarwal B, Ladenstein R, Fitzgerald E, Barr R, Valsecchi M G. New policies to address the global burden of childhood cancers. *The Lancet Oncology.* 14(3);e125-e135
20. You D, Hug L, Ejdemyr S,Idele P, Hogan D, Mathers C, Alkema L. Global, regional and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Inter-agency Group for Child Mortality Estimation. *The Lancet* 2015; 386(10010):2275-2286
21. Burkitt DP. A sarcoma involving the jaws in African children, British Journal of Surgery 1958; 46218-223
22. Burkitt DP, Tunstall M. Common geography as a clue to causation. *Tropical and Geographical Medicine* 1975; 27:262-267
23. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's Lymphoma. *Lancet* 1 1964; 702-703
24. Van den Bosch CA. Is endemic Burkitt's Lymphoma an alliance between three infections and a tumour promotor? *Lancet Oncology* 2004;5(12):738-746
25. Lam KM, Syed N, Whittle H, Crawford DH. Circulating Epstein-Barr virus-carrying B cells in acute malaria
26. Chabay PA, Preciado MV. EBV primary infection in childhood and its relation to B-cell lymphoma development: a mini-review from a developing region. *Int.J.Cancer* 2013;133(6):1286-92
27. Engels EA, Biggar J, Hall HI, Cross H, Crutchfield A , Finch JL et al. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* 2008; 123(1):187-194
28. Mutyaba I, Phipps W, Krantz EM et al. Population-level evaluation of the effect of antiretroviral therapy on cancer incidence in Kyadondo County, Uganda, 1999-2008. *J Acquir Immune Defic Syndr.* 2015; 69(4) :481-486
29. Wabinga H, Nambooze S, Amulen PM, Okello C, Mbus L, Parkin DM. Trends in the incidence of cancer in Kampala, Uganda 1991-2010. *Int J. Cancer* 2014;135(2):432-439.
30. Cook-Mozaffari P, Newton R, Beral V, Burkitt DP. The geographical distribution of Kaposis sarcoma and of lymphomas in Africa before the AIDS epidemic. *British Journal of Cancer.* 1998; 78(11): 1521-8
31. Olp LN, Minhas V, Gondwe C.et al. Effects of antiretroviral therapy on Kaposi's Sarcoma-associated Herpes virus (KSHV) transmission among HIV-Infected Zambian children. *Journal of the National Cancer Institute* 2015; 107 (10)
32. Lee CL,Hsieh KS, Ko YC. Trends in the incidence of hepatocellular carcinoma in boys and girls in Taiwan after large scale Hepatitis B vaccination. *Cancer Epidemiology, Biomarkers and Prevention* 2003;12(1);57-9
33. Shimakawa Y, Lemoine M, Mendy M et al. Population-based interventions to reduce the public burden related with hepatitis B virus infection in the Gambia, West Africa. *Trop Med Health* 2014: 42(2 suppl):59-64
34. Chang MH, You SL, Chen CJ, Liu CJ, Lee CM, Lin SM et al. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20 year follow-up study. *Journal of the National Cancer Institute* 2009; 101:1348-1355
35. Saha V, Love S, Eden T, Micallef-Eynaud P, Mackinlay I. Determinants of symptom interval in childhood cancer. *Archives of Disease in Childhood* 1993;68: 771-4
36. Howard SC, Wilimas JA. Delays in diagnosis and treatment of childhood cancer: where in the world are they important? *Pediatr Blood Cancer* 2005;44:303-304
37. Stefan DC, Siemonsma F. Delay and causes of delay in the diagnosis of childhood cancer in Africa. *Pediatr Blood Cancer* 2011; 56(1):80-85.
38. Poyiadjis S, Wainwright L, Naidu G, MacKinnon D, Poole J. The Saint Siluan warning signs of cancer in children: impact of education in rural South Africa. *Pediatr Blood Cancer* 2011;56:314-316
39. Hunger SP, Sung L, Howard SC. Treatment strategies and regimens of graduated intensity for Childhood Acute Lymphoblastic Leukaemia in low-income countries: A proposal: *Pediatr Blood Cancer* 2009;52:559-565
40. Israels T, Renner L, Hendricks M, Hesseling P, Howard S, Molyneux E. SIOP PODC Recommendations for Supportive Care of Children with Cancer in low-income settings. Pediatr. *Blood Cancer* 2013; 60:899-904.
41. 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
42. Molyneux E, Davidson A, Orem J, Hesseling P, Balagadde-Kambugu, Githanga J, Israels T. The Management of Children with Kaposi Sarcoma in Resource Limited Settings. *Pediatr Blood Cancer* 2013;60: 538-542
43. Israels T, Moreira C, Scanlan T, Molyneux E, Kampondeni S, Hesseling P et al. SIOP-PODC:Clinical Guidelines for the management of Children with Wilms Tumour in low Income settings. *Pediatr Blood Cancer* 2013;60: 5-11
44. Chantada G, Luna-Fineman S, Sitorus RS, Kruger M, Israels T, Leal C et al. SIOP-PODC Recommendations for Graduated-intensity Treatment of Retinoblastoma in Developing Countries. *Pediatr. Blood Cancer*
45. Day S, Hollis R, Challinor JM, Bevilacqua G, Bosomprah E. Baseline Standards for paediatric oncology nursing care in low to middle income countries: position statement of the SIOP-PODC Nursing Working Group. *Lancet Oncology*; 2014 Volume 15:681-682
46. Patte C, Auperin A, Michon J et al. The Societe Francaise d'Oncologie Pediatrique LMB89 Protocol: Highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphoma and L3. Leukaemia. *Blood* 2001; 97:3370-3379
47. Hesseling PB, Njume E, Kouya F, Katayi T, Wharin P, Tammannai M et al. The Cameroon 2008 Burkitt Lymphoma Protocol: Improved Event – Free Survival with Treatment Adapted to Disease- Stage and the Response to Induction Therapy. *Pediatric Hematology and Oncology* 2012;29: 119-129
48. Ngoma T, Adde M, Durosinmi M, Githang'a J, Aken'Ova Y, Kaijage J, et al (+11 other authors). Treatment of Burkitt lymphoma in equatorial Africa using a simple three-drug combination followed by a salvage regimen for patients with persistentor recurrent disease. *Br J Haematol.*2012 Sep;158(6):749-762.
49. Rahiala J, Riikonen P, Kekalainen L, Perkkio M. Cost analysis of the treatment of acute childhood lymphoblastic leukaemia according Nordic protocols. *Acta Paediatr*. 2000 ;89:482-487.
50. World Health Organization Model List of Essential Medicines for Children 5th List April 2015 (amended August 2015)-www.who.int/medicines/publications/essential medicines /en/
51. Robertson J, Magrini N, Barr R, Forte G, Ondari C. Medicines for Cancers in Children: The WHO Model for Selection of Essential Medicines . Pediatr Blood Cancer 2015;62:1689-1693
52. Barr R, Robertson J. Access to cytotoxic Medicines by Children with Cancer: A focus on low and middle income countries. Pediatr. *Blood Cancer* 2015;doi10.1002/pbc.25722.
53. Denburg A, Arora B, Arora RS, Auste C, Bagai P, Barr R, Challinor J, Eden T, Grynzspancholc E, Hoffman R, Link M. Access to essential medicines for children with cancer: a joint SIOP-CCI position statement The Lancet Oncology 2017: Volume 18(January):20-22
54. Eden T, Burns E, Chunda-Lyoka C, Dolendo M, Islam A, Khaing AA and 6 others. Are Essential Medicines Available, Reliable, and Affordable in low –Middle income countries. *Proceedings of the international Society of Paediatric Oncology October* 2015-published on line SIOP 2015 abstract SIOP5-0121
55. Clark F. Rise in online pharmacies sees counterfeit drugs go global. *The Lancet* 2015 ; 386:1327-1328