Chapter 13
Developing World Perspective

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Childhood ALL (cALL), the most common form of childhood cancer, is curable with ~90% becoming long term survivors using contemporary multi-agent chemotherapy. But there is a great disparity in treatment outcome; this high success rate is limited to high income countries (HIC) with little improvements in low and middle income countries (LMIC) over the last 50 years. This inequity is unfortunate because cALL is curable with cheap generic drugs using an appropriately designed treatment protocol, good diagnostic and supportive care, and socio-economic support for the family. Even in the most deprived settings, 30% of cALL can be cured.

However, simply copying intensive treatment protocols from HIC when supportive care is inadequate, exposes children to severe treatment-related morbidity and mortality, increasing costs, and abandonment. To succeed, LMICs need to study the reasons for failure, plan what resources and funding are available, train healthcare professionals on how to deliver appropriate treatment, manage complications using standardized protocols and collect comprehensive data including toxicity and reasons for abandonment. Twining with an aspirant or mentor institution enables training and weekly online conference calls to monitor and discuss patients and problems. Above all, the cure of cALL in LMICs can be achieved through strong partnerships between supportive governments, strong charity, dedicated mentoring institution and a passionate team led by inspiring and visionary leadership. I will explore and summarise practical areas where LMICs may find useful in managing cALL with limited resources.

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13.1 Why the Developing World?

Eighty percent of children with ALL reside in LMICs but account for only for 6.2% cancer expenditures worldwide [1]. ALL is essentially a childhood cancer with peak incidence between 2 and 6 years old. The population in LMICs is young and rapidly growing. With death from diarrheal and infectious diseases decreasing and poverty alleviation programs pulling millions out of extreme poverty, LMICs are ready to tackle cALL. Except for Africa and war-torn south-central Asia, the rising incidence of childhood cancer, falling under-5 year old mortality rates and childhood cancer mortality in LMIC provide the unique opportunity to tackle cALL (Fig. 13.1).

Curing cALL is cost effective. The most effective chemotherapy drugs are generic, available and affordable. Eighty percent of treatment costs are consumed by supportive care especially antibiotics and safe blood components. Resource stratified care appropriate for each LMIC can optimise the treatment outcome and keep costs affordable. Survivors of cALL have normal intelligence and life span, their potential economic returns over the next 60 years of their life easily justify treatment costs.

13.2 Resource-Stratified Care

We know more about cALL than any other cancer. We know the biology of this disease, what is needed to cure and when good supportive care is most critical. Low income countries can cure ~30% of children with ALL with simple protocols that

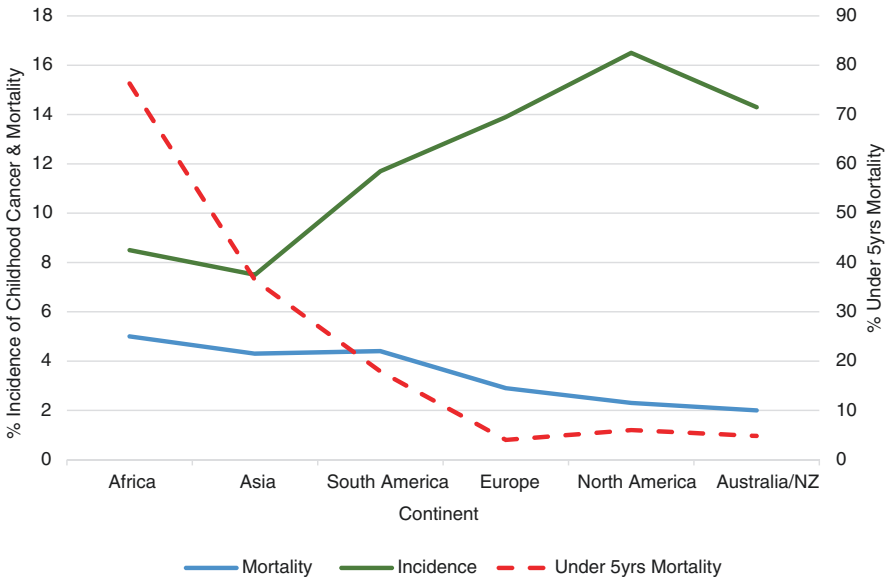

Fig. 13.1 Incidence of childhood cancer and cancer mortality and Under 5-years mortality in 6 inhabited continents in the world. With improved health care, more childhood cancers are diagnosed and fewer cases missed. With lowered under 5-years mortality, most LMICs are poised to improve treatment outcome for childhood ALL. (GLOBOCAN 2012 and World Bank 2015 data)

can be administered by trained general practitioners while middle income countries can cure ~60% through more complicated blocks by trained paediatricians. One way to stratify care is to use the World Bank [2] definition of low (n = 31) and middle-income (n = 104) income countries which have gross national income per capita of <US $1000 and US$1000 to US$12,000 respectively. However, disparity in income and medical resources may differ between provinces and rural versus urban areas in large countries.

13.3 Diagnosis

Most children with ALL present typically from symptoms of pancytopaenia – recurrent fevers from neutropaenia, increased tiredness from anemia, petechiae and mucosal bleed from thrombocytopaenia. Uncontrolled growth of lymphoblasts in bone marrow, lymph nodes, liver and spleen cause bone pain, lymphadenopathy and hepatosplenomegaly respectively. Unfortunately some of these signs and symptoms are similar to dengue fever, malaria and tuberculosis. So diagnosis can be delayed by weeks, placing the child in a worse clinical state. Malnutrition and worm infestations are common, decreasing tolerance to and increasing morbidity of therapy.

cALL is rare. Every child with suspected ALL should be referred to a hospital experienced in diagnosing and managing of cALL. Most provincial hospitals only will see few cases per year and will lack experience and supportive care to best manage them. Diagnosis of ALL [3] requires examination of a bone marrow aspirate by an experienced haematologist with specialised equipment (Table 13.1). Sterile, disposable bone marrow needles should be used to aspirate a diagnostic sample from the posterior superior iliac spine and placed into an EDTA tube, usually an adult FBC tube, to prevent clotting. The bone marrow can then be smeared onto a clean microscopic slide. Bone marrow stains using May-Grunwald Giemsa or Wright-Giemsa stains are recommended as they have good nuclear staining, allowing appreciation of open chromatin and nucleoli and cytoplasmic inclusions.

13.4 Where Should cALL Be Treated in LMICs?

Unlike in HIC where cALL is managed by paediatric oncologists in paediatric cancer centres, in LMIC, cALL can be managed either in a paediatric unit in a general hospital or in a children's hospital or adult cancer or haematology hospital. They can be managed by paediatricians with interest in paediatric hematology-oncology or by adult haematologist focusing on paediatric oncology. Each care model has its own merits and limitations (Table 13.2). In some countries, like India and Philippines, pediatric oncologists in private hospital manage a sizeable number of cALL successfully. These private hospitals have a charity foundation or receive special land rights in return for treating a certain number of poor patients.

Table 13.1 Recommended tests for diagnosis and risk stratification in LMICs

Resource available	Diagnosis	Risk stratification criteria
Basic	Morphology and cytochemistry Chest X-ray for mediastinal mass	NCI criteria NCI Standard Risk: Age 1-10 and WBC <50 Mediastinal mass -> T-ALL Day 8 peripheral blood response ABC <1 BM at Day 15, end induction
Limited	Morphology and cytochemistry Immunophenotyping (restricted panel) DNA index RT-PCR of *BCR-ABL1*, *MLL-AFF1*, and *ETV6-RUNX1*	NCI criteria Immunophenotype (T cell vs B cell) Molecular subgroup Favorable: DNA index >1.16 or *ETV6-RUNX1* Unfavorable: *BCR-ABL1*, *MLL-AFF1*. *DNA index <1* Day 8 peripheral blood response ABC <1 BM at Day 15, end induction
Enhanced	Morphology Immunophenotyping DNA index RT-PCR of *BCR-ABL1*, *MLL-AFF1*, *ETV6-RUNX1*, and *TCF3-PBX1* Cytogenetics for hyperdiploidy >50 or hypodiploidy <44 Fluorescence in-situ hybridisation of chromosomes 4, 10, and 17, and *BCR-ABL1* *Pharmacogenetics for Mercaptopurine metabolism: TPMT and NUDT15 variants*	NCI criteria Molecular subgroups Favorable: DNA index >1.16 or Hyperdiploidy > 50 chr, or triple trisomy 4, 10,17 and *ETV6-RUNX1* Unfavorable: *BCR-ABL1*, *MLL-AFF1, Hypodiploidy < 44 chr* Minimal residual disease measurements by IgH or T-cell receptor rearrangements, flow cytometry, or deep sequencing Pharmacogenetics

In LMICs, working cooperatively on the strengths of each hospital is the way forward. Communication and collaboration as a national group using a common protocol allow easy understanding and transition of care. This may involve centralising cytogenetics and flow cytometry in haematology hospitals. Transferring to children's hospital for paediatric surgical and ICU care for children who developed severe complications may be life-saving.

Rural patients can be followed up in provincial hospitals during maintenance therapy. University Malaya doctors using the Malaysia -Singapore (Ma-Spore) protocol make weekly telephone calls with provincial hospitals to get updated FBC results and progress of children referred out. If parents are Internet savvy or can use smart phone apps like Whatsapp, FBC charts and maintenance doses of mercaptopurine and methotrexate can be communicated easily by them. Good summary of medical records need to be maintained both by patients and hospital. These can be done using chemocards which summarise WBC, ANC, drug doses and schedules. Parents should maintain a large A4 hard cover exercise books where records can be entered and important blood results and protocols pasted. Having a family

Table 13.2 Comparing paediatric versus adult cancer or blood hospitals in LMIC

Type of hospital	Paediatric in General Hospital or Children's Hospital	Adult Cancer Hospital	Adult Blood Hospital
Doctors	Paediatrician focusing on paediatric oncology	Medical Oncologist	Hematologist focusing on paediatric oncology
Funding	Least funded. Charity to raise funds for childhood cancer	Best government funding	Good funding
Diagnosis	Limited BM morphology and cytogenetics	Limited BM morphology, cytogenetics	Good BM morphology, flow cytometry, cytogenetics, molecular
Imaging[a]	US, CT, MRI	US, CT, MRI, PET-CT	Limited US, CT
Blood support	Limited. Need to get blood from blood centres	Good	Excellent. Random platelet units
Supportive care	Paediatric ICU Paediatric dialysis	Medical ICU Adult dialysis	Medical ICU No dialysis
Surgery	Paediatric Surgery	Excellent oncologic surgery	Limited. Transfer to pediatric hospital
No of patients	Overcrowded with mainly general paediatrics including thalassemia or sickle cell disease.	Severely overcrowded	Least crowded

[a]*US* ultrasonography, *CT* Computerised tomography, *MRI* Magnetic resonance imaging, *PET-CT* positive emission tomography with computerised tomography

coordinator employed by foundations who tracks families and compliance and trained to answer common queries, frees the doctor and nurses from non-health care work. The coordinator help apply for financial subsidy, family financial support and housing.

13.5 Improving Outcome Through Reducing Toxic Deaths, Abandonment and Relapse

The overall results for cALL from LMICs are poor because of high incidence of toxic deaths, abandonment of therapy and relapse. Jogjakarta [4] reported a 5-year EFS of 31% with toxic deaths in 16%, abandonment in 15% and relapse in 38% of patients treated on the Indonesian WK-ALL 2000 protocol. Interestingly, relapse rates in LMICs are not more than twice those from HIC. Reducing intensity of therapy will reduce toxicity and abandonment will improve overall outcome.

LMICs have limited supportive care. Less intensive induction chemotherapy using 2–3 non-myelosuppressive drugs is recommended (Table 13.3). Steroid like prednisolone or dexamethasone and vincristine with IT methotrexate can achieve complete morphological remission in 90% of children with ALL. Adding L-asparaginase significantly increase costs and toxicity but may be manageable in centres with good supportive care. In fact, COG, UKALL and Ma-Spore groups

Table 13.3 Proposed protocol for LMICs based on resource

Basic/Low income country	Limited/Middle income country
Induction (two-drug), for 4 weeks Oral Pred 20 mg/m^2/day in three divided doses for Day 1, then 60 mg/m^2/day × 27 days IV VCR 1.5 mg/m^2/dose[a] weekly day 1/8/15/22 IT MTX[b] day 8/15/22	**Induction (3-drug SR; 4 drug HR) for 5 weeks**
	Oral Pred 20 mg/m^2/day in three divided doses for Day 1, then 60 mg/m^2/day × 6 days
	IV VCR 1.5 mg/m^2/dose[a] weekly D1/8/15/22/29
	Oral Dexa 6 mg/m^2/day for 21 days from D8 to 29
	IM L-Asp 6000 U/m^2/dose twice a week Day 8/11/15/18/22/25
	IV DNR 25 mg/m^2/dose on Day 8 for HR patients only
	IT MTX[b] Day 8/15/29
	IT MTX[b] Day 8/11/15/22/29 for CNS 2/3 BMA at Day day 29 to check morphological complete remission
Interim maintenance #1 for 8 weeks Oral MP 37.5–50 mg/m^2/day for 8 weeks (before bedtime) Oral MTX 20 mg/m^2/week for 8 weeks IT MTX[b], weeks 1/3/5/7 BMA at week 1 to check morphological complete remission	**Consolidation (4 weeks)**
	IV VCR 1.5 mg/m^2/dose[a] weekly on Day 1 for SR
	IV VCR 1.5 mg/m^2/dose[a] weekly on Day 1/8/15 for HR
	Oral MP 50 mg/m^2/day for 28 days (before bedtime)
	IT MTX[b] Day 1/8/15
	IT MTX[b] Day 1/8/15/22 for CNS 2/3
Delayed intensification #1 for 4 weeks IV VCR 1.5 mg/m^2/dose[a], day 1/ 8/15/22 Dexa 6 mg/m^2 per day, for 28 days IT MTX[b], days 1 and 15	**Interim maintenance (7 weeks)**
	IV VCR 1.5 mg/m^2/dose[a] every 10 days
	IV MTX 100 mg/m^2 escalating by 25 mg/m^2 every 10 days
	IT MTX[b] Day 31 for CNS 1
	IT MTX[b] Day 1/11/21/31/41 for CNS 2/3
Interim maintenance #2 for 8 weeks Same as interim maintenance part 1	
Delayed intensification #2 for 4 weeks Same as delayed intensification part 1	**Delayed intensification (SR/HR for 7 weeks)**
	IV VCR 1.5 mg/m^2/dose[a] weekly D1/8/15/22
	Oral Dexa 6 mg/m^2/day for 21 days
	IM L-Asp 6000 U/m^2/dose every 3 days for six doses
	IT MTX[b] Day 1/29
	IT MTX[b] Day 1/8/29 for CNS 2/3
	IV CPM 500 mg/m^2/dose on day 29 with IV mesna 500 mg/m^2
	S/C or IV AraC 75 mg/m^2/dose on D29 to 32 and D36 to 39
	Oral MP 50 mg/m^2/day (before bedtime) for 10 days

(continued)

Table 13.3 (continued)

Basic/Low income country	Limited/Middle income country
Maintenance, 4-week block, repeated until 2 years of maintenance Oral MP 37.5–50 mg/m^2/day for 28 days Oral MTX 15 mg/m^2/week, for 4 weeks Oral Dexa 4 mg/m^2/day for 5 days during week 4 IV VCR 1.5 mg/m^2/dose[a] week 4 IT MTX[b] week 4 for first year	**Maintenance (SR/HR), 12-week block, repeated until 2 years of maintenance** Oral MP 50 mg/m^2/day for 28 days Oral MTX 20 mg/m^2/week, for 4 weeks Oral Dexa 6 mg/m^2/day for 5 days during week 1 for SR Oral Dexa 6 mg/m^2/day for 5 days during week 1/5/9 for HR IV VCR 1.5 mg/m^2/dose[a] week 1 for SR IV VCR 1.5 mg/m^2/dose[a] week 1/5/9 for HR IT MTX[b] week 1 for first year

BMA bone marrow aspirate, *Dexa* dexamethasone, *DNR* daunorubicin, *IM* intramuscular, *IV* intravenous, *IT* intrathecal, *MP* mercaptopurine, *MTX* methotrexate, *L-asp* E coli L-asparaginase, *Pred* prednisolone, *VCR* vincristine. DNR can be replaced with IV doxorubicin at the same dose

[a]Maximum dose of vincristine capped at 2 mg

[b]IT MTX dose 6 mg in 3 ml for < 1 year old; IT MTX 8 mg in 4 ml for 1–2 years old; IT MTX 10 mg in 5 ml for 2–3 years old; IT MTX 12 mg in 6 ml > 3 years old

start majority of their patients with only 3 drug induction chemotherapy. Despite this sadly, many LMICs use 4-drug induction with anthracyclines with high induction deaths due to toxicity.

Starting with less intensive therapy has significant advantages. Firstly, tumour lysis syndrome can be managed without risk of acute kidney injury. Adding three additional doses of L-asparaginase in the Indonesian WK-ALL 2000 protocol [5] increased toxicity without improving EFS. Adding IV anthracycline during induction chemotherapy causes severe prolonged myelosuppression, mucositis and need for prolonged antibiotics and blood product support. These cause increased morbidity, deplete family resources and increase abandonment. CCG-105 study showed that intensive 4-drug induction is not better than 3-drug induction if delayed intensification [6] is given.

13.6 Definition of Abandonment

Refusal to start induction chemotherapy or failure to complete ALL chemotherapy will likely cause relapse and death from disease. Abandonment is defined as stopping chemotherapy for > 6 weeks during any phase of ALL protocol treatment. Loss to follow up after completing maintenance therapy is not abandonment and can be censored. LMICs consistently show abandonment > 6% and this is correlated to low national income, high economic hardship and higher out-of-pocket medical payment [7]. For large countries, there may be even differences in abandonment rates between provinces with lower abandonment among city dwellers. Cultural beliefs that cancer is incurable or chemotherapy drugs are poisons reinforce abandonment behaviours.

13.7 Painful Procedures

A main reason for abandonment is perceived suffering. Children are naturally fearful of hospitals and painful procedures. Seeing a sick child screaming from multiple needle sticks and painful bone marrow aspiration and intra-thecal chemotherapy, often leads to abandonment of treatment by the family. Improving family understanding and provision of social and financial support from dedicated social workers are critical in countering such behaviour.

13.8 IV Lines and Central Lines

EMLA cream for needle punctures, IV conscious sedation for painful bone marrow and IT initially are useful. LMICs may only have butterfly needles. Plastic Jelco needles are ideal. Reusing needles is not acceptable as the risks of blood transmission of Hepatitis C and HIV are too high.

Port-a-cath or Hickman lines are expensive and difficult to maintain. Unless staff are trained and has acceptable rates of infections with central lines, these are best avoided in LMICs. Alternative is to place a temporary peripheral IV catheters in the brachiocephalic vein in the elbow. We use a closed system where all the fluids bags are all spiked up at the time of access of the central line (Fig. 13.2). All chemotherapy

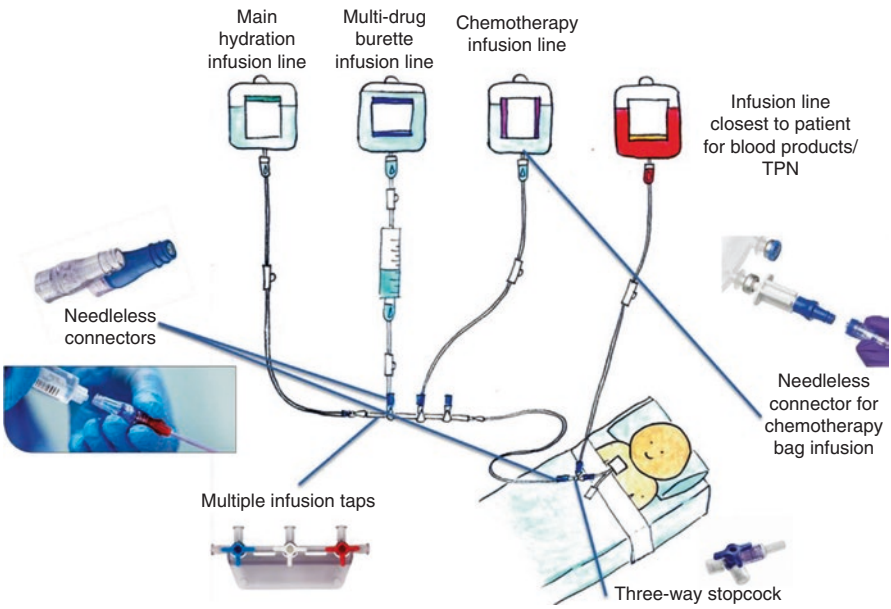

Fig. 13.2 Closed system access to central line using a system of three way stopcock, needless connectors and burettes. The system is set up from the start, minimal opening of the line is needed. Fluids are spiked up in large bags and replaced infrequently

and IV medications are mainly administered in a closed system via a burette and a self-sealing clave that can be cleaned thoroughly using >5 alcohol swabs. This significantly reduces line infections.

IV conscious sedation using IV midazolam 0.2 mg/kg/dose; IV atropine 0.02 mg/kg/dose and IV ketamine 2 mg/kg/dose can be administered safely. Patients should fast for about 4–6 h before IV sedation and pulsed oximetry monitoring should be done during procedure. Parents can be taught to monitor breathing and heart rate post procedure for 1 h. After initial success, some patients can have intrathecal chemotherapy with help of just EMLA cream as local anaesthetic.

13.9 Outpatient Therapy

Inpatient beds are expensive to maintain as it requires supportive infrastructure, doctors and dedicated nurses to run. Outpatient day therapy allows each bed or chemotherapy chair to be recycled a couple of times a day, thus is more cost effective. A dedicated team of 2–3 doctors, 5–6 nurses and a pharmacist to prepare the chemotherapy drugs is necessary. Laboratory results must be available quickly or consultations can be done the day prior to procedure. Chemotherapy drugs are pre-ordered and prepared. Each bed or chair can then be cleaned quickly and recycled 2–5 times each day. Even IT chemotherapy that requires patient to lie flat for 4 h can be done. Governments and insurance should cover outpatient care.

13.10 Halfway Homes

cALL treatment requires around 6–9 months of intensive therapy. Many LMICs are large and sparsely populated with limited transport infra-structure, making travel difficult. Parents sleep in the same bed as the child, cook and eat in the ward and patients are often not discharged because they don't have a place to stay local to hospital. Inpatients wards are overcrowded, with an increased risk of hospital acquired infections. Providing a halfway home is cost-effective and parents can be encouraged and trained to help clean, cook and maintain it with the help of a coordinator.

The non-profit St Jude India Child Care Centre [8] have 18 child care centres. Each centre is run locally with a local team of volunteers who work to a standard operating procedure, which includes instructions on cleaning and maintenance. The key is for local volunteers to be led by a team leader who will raise funds, look for a suitable place to rent and partner local hospitals who care for childhood cancer. Each centre has multiple partitioned rooms with a bed for the mother and child. Each family has a dedicated gas cooker and locker and is given specific rations to cook fresh food for their child. The family stays for about 6 months during the intensive phase of ALL therapy. Parents and patients are taught how to maintain cleanliness, drink boiled water and eat freshly cooked food. This is important as many

children die during maintenance therapy from infections when they return home. Use of mosquito nets and covering food with nets to reduce flies are simple yet effective.

13.11 Infections: Varicella, Measles, TB

Varicella zoster virus is highly contagious and can be severe and even rapidly fatal in children with ALL. Especially in tropical LMICs, many children and even their parents are not immune to varicella. For example, in Guatemala, the incidence of varicella infection in the National Unit of Pediatric Oncology is 23.4 per 1000 person years with a median age of 5.2 years with 14% requiring critical care and a 3.4% mortality [9]. In Singapore, despite varicella vaccination, 32% cALL are seronegative with another 13% losing their varicella immunity after treatment. Patel et al. reported similar frequencies [10]. It is common to have large varicella outbreaks in the LMIC hospitals. Post exposure prophylaxis with oral aciclovir 200 mg/dose (<2 years old) or 800 mg/dose (>2 years old) qds can be used in LMIC centres instead of varicella hyperimmune globulin [11]. As many parents lack immunity to varicella, active varicella vaccination of mothers can be effective with little risk of spread.

In many LMIC, dengue fever and even recently Zika virus are common. Many patients are mis-diagnosed with recurrent dengue hemorrhagic fever when they present with fever and severe thrombocytopaenia causing treatment delay. After dengue or varicella infections patients have prolonged myelosuppression, requiring treatment interruptions and lower doses of chemotherapy. Worms like Ascaris can cause bowel obstruction. Routine deworming is encouraged in LMIC especially when patients are from rural areas.

Although measles vaccination is mandatory and provided free of charge in LMICs, not all children seroconvert. Due to misconceived fears of autism, contamination of porcine source in Muslim countries, fake vaccines and improper vaccine storage, outbreaks of measles infections are common in LMICs. As immunocompromised patients may present with fatal measles pneumonitis without even skin rash, a high index of suspicion is needed. All centres should maintain an up-to-date register of whether their patients have been vaccinated or are immune to varicella and measles.

13.12 Drugs Reliability of Supply: Generic Drugs, Drug Registration

Despite most drugs being included in the WHO List of Drugs, shortage of chemotherapy drugs often plagues LMICs. In 2016, Indonesian government misguided by banned mercaptopurine, which was apparented used for therapeutic abortion, limiting access to one of the most important drug in ALL. Hospitals often lack a good pharmacy to track the availability of drugs and their budget may run out by end of

financial year. Families often have to buy their own drugs from private pharmacies outside the hospital. Pharmaceutical companies lack motivation to register and import chemotherapy drugs used in cALL in LMICs as these are cheap generic drugs. Health ministries are often slow to approve import of drugs. Fortunately common drugs like vincristine, prednisolone/dexamethasone are commonly available and can be sourced from many generic making companies. L-asparaginase, mercaptopurine and oral and preservative free intra-thecal methotrexate are more limited. Foundations should try to coordinate stockpiles and transport of drugs from different countries. In such emergency shortages, standard regulatory rules should be relaxed. The Max Foundation has successfully made available imatinib from Novartis for LMICs.

13.13 Training Doctors and Nurses

Training families on management of fever, side-effects of treatment, administration of medications like steroids with food and mercaptopurine is best on an empty stomach 2 h after dinner and not with milk, is essential for the optimal delivery of treatment. A standardized schedule for the whole hospital e.g., cotrimoxazole is given BD on Monday and Tuesdays while oral MTX is given on Fridays. Similar to asthma action plan, there should be an ALL action plan. Protocol copies should be printed, completed and filed in each patient's case notes. A hard cover book should be provided to families with follow up notes and results in them.

Treatment protocol should be simple. For example, the Indonesian ALL protocol has only Standard risk and High risk protocols, each protocol condensed into two pages which the family can carry to consultations. Treatment is protocolized, to ensure a minimum standard and allow identification of gaps when reviewed systematically. A team of leaders with local experience are involved in designing a practical protocol. Random, unsubstantiated changes, which confound analysis and future improvements, should be avoided. As most of LMICs doctors lack in depth training in delivering chemotherapy, the most effective protocols are probably use limited number of drugs that are not myelosuppressive and in fixed repeated combinations. This allows easy understanding and management of side-effects.

A simple concept is to do the possible first. LMICs can start with treating children with NCI standard risk, especially those from the city. This reduces the problems of transport infrastructure and treatment abandonment. Children from rural areas are at increased risk of infections due to lack of clean water, long distance to hospital, higher risk for fungal infections from atap roofs and infections like malaria and dengue.

It is important to collect baseline and survival data. Data provide ways to identify the critical gaps that then can be tackled systematically and reassessed if the intervention is successful. For example, if abandonment due to lack of money, transport and housing can be addressed by improved financial support of even paying families such as by providing coupons for public transport and half-way houses.

13.14 Staff

Majority of the doctors and nurses from LMICs are not trained in pediatric oncology. Doctors lack mentors who have proper training to manage ALL and its complications. Similarly nurses may not appreciate the importance of aseptic technique and how to administer chemotherapy and antibiotics. Training the trainer who are senior members of the team is critical. There is a need to develop a standardized curriculum from which adaptation and translation can be done. In fact, St Jude Global [1] is planning to set up a school for paediatric oncology training where doctors, nurses and health care professionals can be trained and certified.

Doctors and nurses from LMICs in government hospitals are badly paid. Successful programmes start with raising funds to pay the salaries of a leader, dedicated team of senior doctors and nurses (Table 13.4). Experienced staff to manage the sickest children cannot be retained without the adequate remuneration.

Advances in affordable technology – emails, web conferencing, courier, Internet-enabled data repository like RedCap – can overcome current limitations and

Table 13.4 Important elements for setting up an ALL programme in developing countries

Leader – well trained in pediatric oncology, respected, leadership qualities, consensus builder, able to get a team running, mature, visionary – able to project needs to future, communicator, fund raiser
Team – paediatrician, haematologist specialist, paediatric oncology trained nurses. Nurses from developing countries tend to be less trained and do not speak good English
Coordinator – administrator
Facility – inpatient – dedicated paediatric oncology unit including isolation rooms– reduces infections from general paediatric cases like pneumonia, viral infections. Lots of wash basins. Well maintained clean, well ventilated facility
Outpatient facility – allow right siting of care, recycling outpatient beds which are less expensive to maintain
Cancer pharmacy – reconstitution of drugs, checking drug doses and route of administration. Keep track of drugs to avoid shortages
ICU including ventilator support, haemodialysis and continuous monitoring
Blood bank – preferably 24/7 support, safe screened blood components including platelets, fresh frozen plasma and RBC concentrates
Laboratory support – FBC, Chemistries, Blood culture, Fungal culture
Diagnostic imaging – Ultrasonography, CT scan, MRI, PET-CT scan, Echocardiography
Support – community support like children's cancer foundation – providing psychosocial care for family, family mentors by survivors – able to overcome cultural and non medical issues, fund raising, covering costs of chemotherapy US$15,000 with family support for transport US$6000. Public and health professional education
Governmental support – provision of hospital infrastructure, drug approval, funding
Transport and communications infrastructure. – Prepaid bus tickets
Building half way houses for out of town families to stay during intensive phase of therapy
Funding – initial start up then with time local foundations take over
Twinning with aspirant centres – St Jude Global Program
Mentorship with leaders – provide guidance, consultations training, weekly web-based conferencing. Adaptation of protocol to local context

significantly change care. Unstained bone marrow slides can be shipped by courier or mail to reference centres where they can be properly stained, scanned and uploaded for review by volunteer expert haematologists. Flow cytometry plots can be reviewed on line. Molecular tests can be carried out on dried samples on FTA cards or fixed, unmounted, unstained glass slides.

What we need is a non-intensive, well-tolerated backbone protocol that can be easily used in resource-limited countries. Unfortunately, even the IBFM ALL-Intercontinental (ALL-IC) protocol requires intensive resources outside the reach of most LMICs. The developing world needs to learn to draw up a cost-effective, resource-suitable protocol with the help of the leaders of ALL. The free exchange of experience through the International BFM meetings, Ponte de Legno meetings and publications in English literature have done a lot to rapidly learn how to treat ALL.

13.15 Ethics, IRBs and Databases: Avoiding Unnecessary Excessive Regulations

Currently even data collection study requires approval by institutional review boards (IRB). This is unfortunate as hospitals in LMICs often lack IRBs. Doctors who are already overwhelmed with clinical work do have time to submit unnecessarily complex forms and applications. Applying HIC ethical standards to LMICs which lack the infrastructure and manpower is unhelpful. Champions for each national cooperative groups can design a common universal simple consent form that can be used for all hospitals.

Imposing excessive regulation like personal data protection and complicated ethics and health regulatory requirements will hamper early effective implementation of ALL treatment in developing countries. An example is the now defunct Pediatric Oncology Database (POND) which successfully supported multiple paediatric cancer centres to collect simple data and survival outcomes. But concerns about personal data security have unfortunately undermined an otherwise simple to use and intuitive online database. New databases like ReDCap will help but they require more specialized training to use.

In summary, cALL is a curable disease even in developing countries. Resource-stratified treatment protocols, identifying an inspiring leader, training a dedicated team of doctors and nurses and provision of socio-economic support for families of children with ALL are some of the critical components of a successful programme. Copying resource-intensive protocols and ethics requirements from HIC are inappropriate.

References

1. Rodriguez-Galindo C, Friedrich P, Alcasabas P, et al. Toward the cure of all children with Cancer through collaborative efforts: pediatric oncology as a global challenge. J Clin Oncol. 2015;33:3065–73.
2. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and--lending-groups. Accessed 17 Aug 2016.

3. Yeoh AE, Tan D, Li CK, et al. Management of adult and paediatric acute lymphoblastic leukaemia in Asia: resource-stratified guidelines from the Asian Oncology Summit 2013. Lancet Oncol. 2013;14:e508–23.
4. Widjajanto PH, Sumadiono S, Cloos J, et al. Randomized double blind trial of ciprofloxacin prophylaxis during induction treatment in childhood acute lymphoblastic leukemia in the WK-ALL protocol in Indonesia. J Blood Med. 2013;4:1–9.
5. 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 WK-ALL-2000 protocol. J Pediatr Hematol Oncol. 2013;35:597–602.
6. Tubergen DG, Gilchrist GS, O'Brien RT, Coccia PF, Sather HN, Waskerwitz MJ, Hammond GD. Improved outcome with delayed intensification for children with acute lymphoblastic leukemia and intermediate presenting features: a Childrens Cancer Group phase III trial. J Clin Oncol. 1993;11:527–37.
7. Friedrich P, Lam CG, Itriago E, Perez R, Ribeiro RC, Arora RS. Magnitude of treatment abandonment in childhood cancer. PLoS One. 2015;10:e0135230.
8. http://www.stjudechild.org/. Accessed 17 Aug 2016.
9. Brown AE, Asturias EJ, Melgar M, Antillon-Klussmann FA, Mettler P, Levin MJ. Incidence and consequences of varicella in children treated for cancer in Guatemala. World J Pediatr. 2016;12:320–6.
10. Patel SR, Bate J, Maple PA, Brown K, Breuer J, Heath PT. Varicella zoster immune status in children treated for acute leukemia. Pediatr Blood Cancer. 2014;61:2077–9.
11. Bate J, Chisholm J, Skinner R, Breuer J, Ramsay M, Wheatley K, Hambleton S, Heath PT. PEPtalk: postexposure prophylaxis against varicella in children with cancer. Arch Dis Child. 2012;97:853–4.