bjh global perspectives

Precursor B-cell acute lymphoblastic leukaemia—a global view

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Summary

As haematologists, we always seek to follow standardised guidelines for practice and apply the best treatment within our means for our patients with blood diseases. However, treatment can never follow an exact recipe. Opinions differ as to the best approach; sometimes more than one treatment approach results in identical outcomes, or treatments differ only by the manner in which they fail. Furthermore, the haematologist is faced with constraints relating to the local economic environment. Patients too are not the same the world over. Early presentation is commoner in the developed world, as is the patient's understanding of the disease process. This in turn has an impact on the way patients are managed, the rigorousness of patient adhesion to the treatment schedule and the outcome. Here we take a look at the precursor B-cell acute lymphoblastic leukaemia in an adolescent in a range of different settings from low- to high income countries with widely differing challenges for diagnosis, therpy and follow-up. For these reasons, given the same starting conditions, patients will be treated differently according to the institute and the country they are in. Experts from around the world have been tasked to describe their management plan and rationale for a specific disease presentation. Here they explore the management of precursor B-cell acute lymphoblastic leukaemia (pre-B ALL) in five different institutions worldwide with a focus on those with more or less strained economies. We end with a conclusion from an expert in the field comparing and contrasting these different management styles and considering their merits and limitations.

Keywords: precursor B-cell acute lymphoblastic leukaemia, treatment, blood diseases.

Tackling ALL in childhood and focusing on low- to medium-income countries entails the most complicated issues in this series, and choices and omissions had to be made in preparation for the receival of the contributions. Thus, reflecting upon the heterogeneity in health systems and medical traditions, the contributions herein are very different in length, reflecting the status of therapy as well as the diverse history by which the presently employed cytoreductive protocols were arrived at in the widely different settings. Regarding the latter, we have chosen Brazil to show how protocols have evolved concurrently with the expansion of multicentre collaborations. Along these lines, Ireland was chosen as an example of a high-income country to illustrate what might be considered as a gold standard of approach to a patient like the present one.

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Moreover, the purpose of these endeavours is to give the reader the present state of caring for such patients and not to look forward to what might happen in the future. This could perhaps be a subject for a separate wider perspective contribution. Furthermore, space constraints do not allow us to look at an array of other issues such as biobanking, the existence and extent of registries, and the inclusion into centres of excellence for the different locations. We nevertheless hope that this exercise brings home to practicing clinicians that there is more than one 'right' way to manage patients. The case history and questions posed to the experts are shown in Boxes 1 and 2, and their responses are summarised in Table I. There are always things to learn from the way other experts practice. Moreover, there is much to learn from our colleagues working in strained economies. Overall, this exercise teaches us that we should be nuanced in our perception of how and why treatments differ worldwide.

Box 1. Case history (P Hokland)

A 15-year old girl has experienced progressive fatigue during the preceding five months. Her menstrual periods, which started two years previously, have become irregular within the last year and her last one was three months ago. During the last two months she has experienced night sweats. Her local physician finds her of normal height and weight, but pale. She displays normal vital signs except for a pulse of 80 beats per minute. A complete blood count on a local haematology machine reveals a Hb of 6·4 mmol/l, a platelet count of 130×10^9/l and a leukocyte count of 68×10^9/l.

She is referred to a tertiary department.

Box 2. Questions for the panel (P Hokland)

-Q1: Please indicate what diagnostic tools are presently available at your institution and how you would employ them for this patient.
-Q2: Assuming that a diagnosis of pre-acute lymphoblastic leukaemia (pre-ALL) has been established, please indicate the possibilities at your institution/country for fertility preservation (oocyte cryopreservation which employs delays in treatment commencement or ovarian tissue cryopreservation which does not).
-Q3: Please indicate how you would prognosticate for the patient and what cytoreduction/induction chemotherapy you would commence with special emphasis on whether she should be enrolled in a paediatric centric or an adult protocol. Please also state how overall cytoreduction strategies have changed during the latest decade at your institution.
-Q4: Your treatment induces complete remission (CR) in your patient. Please indicate how this condition is defined at your institution and how you would proceed with cytoreduction. In addition, at which timepoints is disease status checked and clinical decision-making crucial, e.g. in relation to allogeneic transplants?
-Q5: If this patient remains in CR, please indicate how and where you would manage long-term follow-up. In particular, how would you advise her, if she wants to become pregnant (irrespective of whether she has had fertility preservation carried out or not).

The perspective from Brazil (MLM Lee)

Q1 diagnosis

Epidemiological studies have demonstrated that ALL has a higher incidence rate in the Latino population with outcomes in both paediatric cases and adults drastically worse than international standards. The underlying cause of these observations is unknown, although several hypotheses have been postulated including disparities in socioeconomic status, environmental risks, inherited genetic mutations, or a combination of factors.[1,2]

In Brazil, the geographical distribution of ALL is of particular interest. The overall age-adjusted incidence rate (AAIR) of ALL in children is about the same as in Non-Hispanic White Americans (35·2 per million × 35·6 per million); the highest incidence rate (56·6 per million) is observed in children of Native American ancestry in the Brazilian North Region (Brazilian Amazon region).[3,4] In contrast, along the Atlantic coast in Brazil, the incidence of ALL ranges from 21·6 to 43·6 per million.[1]

The Brazilian Cooperative Trials for Treatment of Acute Lymphoblastic Leukemia in Children (Brazilian Pediatric Acute Lymphoblastic Leukaemia Cooperative Treatment Group, GBTLI) was initiated by Brandalise, Odone, and Pereira in 1980, and six consecutive trials were performed (GBTLI LLA 80, 82, 85, 93, 99, 2009 studies). Since then, significant advances have been made in paediatric ALL in our country, from improvements in diagnostic tools to a progressive increase in survival curves, from an event-free survival (EFS) of 24·8% ± 3% and an overall survival (OS) of 34·1 ± 3·9% in GBTLI LLA 80 to 66·1 ± 1·7% and 70·0 ± 1·6% in GBTLI LLA 93.[5,6]

In general, presently patients with the disease will be handled in an inpatient setting, given that Brazil is a low-income country and intensified support for patient and family is usually needed.[7] A recent survey realised by the Brazilian Pediatric Acute Lymphoblastic Leukemia Cooperative Treatment Group (GBTLI LLA) (P. Godinho, unpublished data) found that 97·4% of services registered in the Brazilian Society of Pediatric Oncology (SOBOPE) for the treatment of paediatric ALL perform cytomorphological analysis of bone

Table I. Country-wise responses to questions regarding the diagnosis, therapy and follow-up of a 15-year-old girl.

	Diagnostic tools at diagnosis	Ovarian tissue preservation	Prognostication and initial therapy	Definition of CR and actions upon accomplishment	Management of long-term follow-up
Brazil	CBC, PB and BM smears IP Cytogenetics qPCR or FISH CSF cytospin analysis *Specialised analyses usually outsourced*	Not available	NCI stratification CNS status LR and HR rearranged MRD response D15/D19 Pre-phase with prednisone with IT. Then Brazilian protocol GBTLI with a VCR, DNR, L-ASAP backbone plus MTX IT	Blast cells on BM smear less than 5% and signs of peripheral blood count recovery MRD response end induction to HR stratification, qPCR intended, but to be replaced by FCM MRD positive at end of consolidation phase defines alloHCT	Onco-haematologist monthly in first 6 months; bi—monthly in second semester. Every 3 months in second year. Every 6 months in third year tapering to annually. Endocrinologist, cardiologist, ophthalmologist, dentist, gynecologist schematised Others professionals on demand
India	CBC, PB and BM smear and a LP IP Cytogenetics FISH qPCR, including for Ph1 chromosome *Specialised analyses not available in most centres*	Though cryopreservation facilities are available in selected centres, expertise in oocyte cryopreservation methods are very limited and cost-intensive	Paediatric-inspired ALL prognostication and treatment in the AYA group She will receive the InPOG-ALL-15-01 (Intermediate risk) with protocol with a VCR, DNR, L-ASAP backbone plus MTX IT	BM examination with adequate cellularity and <5% myeloblasts with no lymphoblasts, absence of blasts in CSF MRD by BM. In Ph^+ ALL, MRD by qPCR is done additionally. Patients with poor prednisolone response, CNS disease, post-induction and HR transition to the HR protocol	Controls every 3 months for the first 2 years, every 6 months between the 3rd and 5th years, and annually thereafter. Long-term toxicities and late effects are monitored by clinical evaluation, with a focus on musculo-skeletal challenges in the near-term followed by metabolic syndrome, endocrine, and cardiac effects on longer follow-up
Ireland	CBC with blood smear BM aspirate for Cytomorphology IP by eight-colour FCM Cytogenetics, FISH and SNP array BM trephine biopsy histology and immunohistochemistry) MRD assessment by RQ-PCR (Ig/TCR) TPMT genotyping	Oocyte cryopreservation possible	NCI—HR pre-B ALL. Initial treatment allocation will be following risk-directed UKALLK 2019 Interim Guideline with VCR, DNR, L-ASAP (pegylated) backbone plus MTX IT	MRD monitoring has redefined remission in ALL. Further stratification will be by cytogenetic risk and MRD level at D29 and recovery from consolidation at week 14. After MRD transition to either UKALLK 2019 regimen B (LR) or regimen C (HR), i.e. augmented BFM	Transition into a dedicated AYA Cancer Unit for survivorship/long-term follow-up
Mali	CBC, blood film and bone smear for morphological evaluation	Not available	Age, leukocyte count, bulky disease, CNS signs, response to pre phase steroids French-African Pediatric Oncology Group Protocol 4 drug VCR, DNR, L-ASAP backbone plus MTX IT	BM assessment at D 42: Blast cells on BM smear less than 5% concomitantly with a neutrophil count more than 1×10^9/l and a platelet count of more than 100×10^9/l. Intensification with repeated 4-drug regimen plus high-dose MTX IV	Control with clinical review and CBC every 2 months for the first year after maintenance therapy, every 3 months for the second and third year and then every year until age 18. She will be referred to adult haemato-oncologist

Table I. (*Continued*)

	Diagnostic tools at diagnosis	Ovarian tissue preservation	Prognostication and initial therapy	Definition of CR and actions upon accomplishment	Management of long-term follow-up
Tanzania	CBC PB smear FCM CSF cytospin BM analysis only if PB smear or flow non-diagnostic	Not available	Age; African ethnicity; highest pre-treatment white cell count; ALL cell subtype; Bulky disease, CNS involvement & response to treatment of same; testicular involvement; Response to pre-phase steroids; D28 MRD analysis (FCM) UKALLK 2003 plus steroid pre-phase based cytoreduction (PEG asparaginase replaced by L-ASAP due to cost; triple IT therapy instead of monotherapy)	Assessment at Remission Induction D28: MRD less than 0·1% sensitivity: continue current treatment MRD 0·1–5%: escalate to UK ALL2003 regimen C treatment; MRD <5%: palliate with maintenance or oral etoposide/cyclophosphamide treatment for B-cell; continue to Augmented Consolidation for T-cell. Assessment at end of Augmented Consolidation (where RI MRD was positive) MRD-negative: continue treatment MRD-positive: palliate	Maintenance treatment given at shared cared sites. Follow-up off treatment every 3 months X2 years and 6 months X3 years and annually thereafter - with clinical review and CBC. Shared care sites report on children at weekly virtual meetings with National Hub. No other special investigations offered routinely
Thailand	CBC, blood smear BM aspiration for morphology BM FCM for AML, ALL BM cytogenetics BM core biopsy BM RT-PCR for BCR–ABL1 P190 and P210	Not routinely done	Ph-negative ALL: VHR paediatric-based ALL protocol (ThaiPOG-ALL-13-3) VCR, DOX, L-ASAP backbone plus MTX IT $Ph1^+$ ALL: Ph^+ ALL protocol (ThaiPOG-ALL-1304) VCR, DOX, L-ASAP backbone plus triple ITimatinib 340 mg/m^2	CR: BM lymphoblast is less than 5% by morphology and FCM Indications for HSCT: Post-induction assessment D29 shows either induction failure, hypodiploidy cytogenetically or Ph1+	CBC 1st year: every 1–2 months 2nd year: every 2 months 3rd year: every 3 months 4th year: every 6 months 5th year and later: yearly Optional as clinically indicated: 1st year: BMA, BUN, Cr, AST, ALT, echo, EKG, LP Reproduction aspect: avoid pregnancy within the first 6-month period following chemotherapy

ALL, acute lymphoblastic leukaemia; alloHCT, allogeneic stem cell transplantation; ALT, alanine aminotransferase; AML, acute myeloid leukaemia; AST, aspartate aminotransferase; AYA, adolescents and young adults; BFM, Berlin–Frankfurt–Münster; BM, bone marrow; BMA, bone marrow aspirate; BUN, blood urea nitrogen; CBC, complete blood count; CNS, central nervous system; Cr, creatinine; CR, complete remission; CSF, cerebrospinal fluid; D15, day 15; DNR, daunorubicine; DOX, doxorubicine; EKG, electrocardiogram; FCM, flow cytometry; FISH, fluorescence *in-situ* hybridisation; HR, high risk; HSCT, haematopoietic stem cell transplant; Ig/TCR, immunoglobulin/T cell receptor; IP, immunophenotyping; IT, intrathecal; IV, intravenous; L-ASAP, L-asparaginase; LP, lumbar puncture; LR, low risk; MRD, minimal residual disease; MTX, methotrexate; NCI, National Cancer Institute; PB, peripheral blood; Ph, Philadelphia; qPCR, quantitative polymerase chain reaction; RI, reduced intensity; RT-PCR, real-time qPCR; SNP, single nucleotide polymorphism; TMPT, thiopurine methyltransferase; VCR, vincristine; VHR, very high risk.

marrow as well as immunophenotyping. In addition, 92·2% perform cytogenetics and 87% have access to some type of diagnostic molecular biology [real-time quantitative polymerase chain reaction (RT-qPCR)] or fluorescence *in-situ* hybridisation (FISH). However, 24·6% of these replied that neither *ETV6–RUNX1* rearrangements nor *PBX1–TCF3* were routinely performed. Another relevant fact reported is that of the 77 registered centres in SOBOPE that responded to the survey, only 23 (30%) perform the diagnostic examinations in an in-house setting, implying that there is a great challenge in a country of continental dimensions such as Brazil in terms of dissemination of the relevant methodologies.

Considering the case in question, the tools that are usually performed in Brazil to diagnose acute leukaemia include cytologic examination of the bone marrow (BM) and peripheral blood (PB) and immunophenotyping is mandatory. Conventional cytochemistry is not routinely required, but may be helpful in some Brazilian services.

In addition, conventional cytogenetics with high-resolution G-banding is the gold standard, and molecular genetics (qPCR or FISH) to investigate prognostically important fusion genes (*ETV6–RUNX1*, *TCF3–PBX1*, *BCR–ABL1*) is recommended for all cases. In contrast, the investigation of Philadelphia (Ph)-like ALL (also seen at higher rates in Latinos), intra-chromosomal amplification of chromosome 21 (iAMP21) and *IKAROS* deletions are not performed routinely considering the age of the patient.[1,8,9] Neither is the investigation of *GATA3* single nucleotide polymorphisms, which are also increased in Philadelphia chromosome-positive (Ph^+) Hispanics.[10]

Prior to chemotherapy, standard evaluations include blood chemistry profiles, viral serology, echocardiography and abdominal ultrasound. In addition, dental examination is recommended, but not performed in all centres.

Q2 Fertility preservation

Counselling about preserving one's fertility should be offered to all patients.[11] Despite that, in the Brazilian Public Healthcare System, which is responsible for the treatment of the vast majority of patients, female fertility preservation is not widely available at the present time. Moreover, even within private services, this option is not easily accessible for nearly all patients.

Q3 Prognostication and induction

According to National Cancer Institute (NCI) risk stratification, this patient has the initial risk classification of high risk (both by age and initial white-cell count). The outcome for older children, especially adolescents, has improved significantly over time. Five-year survival rates for adolescents aged 15 to 19 years increased from 36% (1975–1984) to 72% (2003–2009).[12] The risk stratification for B-cell precursor leukaemia based on NCI criteria was introduced in Brazilian Protocol GBTLI LLA 99 and continues in GBTLI 2009.

Given that it has become clear that in adolescents and young adults (AYA) ALL has superior survival when treated with paediatric-based regimens, this has led to their adoption by an increasing number of adult centres.[13–15] Unfortunately, in Brazil, one of the important features of the health system is that all patients older than 13 years of age will be referred to adult departments/centres, where treatment is often inadequate for this group of patients.

The strategies for cytoreduction/induction in Brazilian GBTLI protocols changed (GBTLI 80, 82, 83, 93, 99) from absence of a pre-phase, to the introduction of a pre-phase with prednisone (60 mg/m²/day × 7 days) and one methotrexate (MTX) IT administration in the latest study (GBTLI LLA 2009). Despite cytoreduction, the induction death rate in GBTLI 2009 (6·2%) was similar to that in the previous GBTLI study (GBTLI ALL 99: 6·7%) and higher than in GBTLI ALL 85 (2·6%) and GBTLI ALL 93 (3·2%), reflecting a more intensive induction phase.[5]

The two studies conducted in the 90s, GBTLI 93 and 99, included a total of 2 237 patients. These studies introduced the concept of modern childhood ALL therapy in Brazil, with the use of high-dose methotrexate (HDMTX), the intensification of post-consolidation therapy, the use of prophylactic central nervous system (CNS) radiotherapy just for the high-risk (HR) group, and a reduction in maintenance therapy regimen for 18 months. The complete cytogenetic response (CCR) rate observed was 95·7% and 92·1%, respectively, with an EFS and OS of 66·1% ± 1·7% and 70% ± 1·6% in GBTLI 93, and 67·9% ± 1·6% and 71·5% in study 99. Simultaneously, a reduction in death rates in complete remission (CR) from 7·5% to 4% was observed. Of interest, there was a significant improvement in the EFS for T-cell-derived ALL from 48·6% ± 5·8% in study 93 to 65·9% ± 4·1% in study 99. In GBTLI 2009, patients stratified as NCI low risk were assigned to receive either continuous 6-mercaptopurine (6-MP) and weekly MTX or intermittent 6-MP with intermediate-dose MTX, as maintenance treatment. The randomised trial comparing two different maintenance regimens for patients with LR ALL demonstrated that children treated in an intravenous (IV) MTX/intermittent 6-MP schedule had lower severe grades 3 and 4 of hepatic and haematologic toxicities and a lower death rate in CR (2%) than those receiving the standard continuous schedule (6%). Boys allocated to the intermittent regimen had significantly better EFS than those receiving the continuous schedule.[5,16]

In 1994, an international partnership was initiated between Instituto de Medicina Integral Professor Fernando Figueira, a public paediatric hospital in Recife, and St Jude Children's Research Hospital. Thus, during the period from April 1997 to December 2002, patients were treated according to the St Jude Total XIIIB protocol. These actions led to a significant increase in survival from 47% to 63% over a 10-year period.[17] From December 2005 to June 2015, the newly diagnosed ALL patients were treated using the uniform

guidelines of the Recife ALL pilot study (RELLA-05). A five-day prednisone pre-phase was introduced with the objective of initial clinical stabilisation of the patient; intrathecal (IT) therapy was postponed to the fifth day after the beginning of treatment, thus avoiding an invasive procedure in the period of greater clinical instability and minimising traumatic punctures with consequent contamination by blasts.[18]

Q4 Definition of CR and follow-up

In the current Brazilian protocol, CR is defined by the absence of disease-related symptoms, less than 5% of blasts in a BM smear (confirmed by immunophenotyping analysis), and signs of PB count recovery at the end of the induction phase. The GBTLI LLA 2009 protocol introduced several changes to the previous study, defining distinct timepoints to measure treatment response. The blast count on D8 was incorporated as a risk-stratifier; the evaluation of minimal residual disease (MRD) by flow cytometry (FCM) on day 15 (D15) and by RT-qPCR on D35 was introduced as standard for risk stratification, focusing on the speed of response as an important prognostic factor establishing the concept of fast responder and slow responder. D15 fast responder MRD < 0.01% defines a very-low-risk group pre-B ALL (8·2%), who will receive a less intensive induction. In contrast, the slow responder group displays an MRD ≥ 10% (21·5%), which will be allocated to more intensive therapy [detailed in the GBTLI LLA 2009 Nov 2018 report (unpublished)]. At the end of induction (four weeks of chemotherapy), patients with MRD levels ≥ 10^{-3} were planned to be referred to blood and marrow transplantation (BMT). However, since MRD by PCR was not feasible in most paediatric centres, this option could not be carried out stringently, and in the upcoming study (GBTLI LLA 2021), MRD will therefore be performed by FCM.

Q5 Long-term follow-up

Brazilian healthcare is notoriously heterogeneous in quality. Structured and well-equipped cancer centres are located mostly in the southeastern and southern states. The management of survivors of childhood cancer is even more disparate: although most of the country struggles with cancer screening and detection, some regions have pioneered cancer survivorship programmes, offering multidisciplinary long-term follow-up since the late 90s, and in this context, patients have access to all medical specialties, i.e. endocrinologist, cardiologist, ophthalmologist, gynaecologist, dentist, and others specialist professionals without additional cost. Thus, in most of the Brazilian paediatric oncology services, only the paediatric haematologist/oncologist continue with this follow-up.[19] The clinical returns are performed monthly in the first six months, bi-monthly in the second semester; every three months in the second year, every six months in the third year and then yearly until 10 years off treatment.

We used to refer the patients to a gynaecologist to choose the best contraceptive method in an effort to avoid pregnancy during the first year after treatment was completed. However, being a low-income country with different social-cultural issues, it is not uncommon that patients become pregnant soon after treatment is completed.

The perspective from India (VS Radhakrishnan and M Chandy)

Q1 Diagnosis

India has a young population and a large proportion, 44%, belong to the 0–24-years-old age group [India, in The World Factbook (Internet). CIA.gov. 2021 (cited June 9, 2021_; available from: https://www.cia.gov/the-world-factbook/countries/india/#people-and-society]. It is estimated that annually 75 000–100 000 individuals in this group are diagnosed with cancer, and leukaemias are the most common, accounting for more than 27% of all diagnosed cancers.[20] A low middle income country (LMIC) economy with a 'real (per-capita) gross domestic product (GDP, estimated 2019)' of $ 6700, an annual healthcare expenditure less than 4% of the GDP, a physician density of 0·86 per 1000 population, and a limited number of trained oncology professionals, India has significant limitations in the delivery of optimal cancer care for all.[21] Despite improvement in healthcare services in the past few decades, more than 80% of Indians do not have healthcare insurance. A significant proportion of the insured individuals have limited coverage and often require out-of-pocket expenditure for cancer care.[22] The situation is often such that low-income households, mostly uninsured, very often resort to distress means to finance cancer care.[23] In the absence of a well-structured healthcare system, an organised referral pathway for cancer care is nearly non-existent. The care of the young with cancer, leukaemia in particular, is often a story of 'missed opportunities'. A combination of factors is responsible for this and includes, among others, late presentation with a high tumour burden, delayed diagnosis, treatment denial or abandonment, higher treatment toxicity due to undernutrition and poor supportive treatments, and suboptimal care.[24] There are only a limited number of tertiary-care centres with the expertise to treat ALL of the young in organised treatment protocols, in a multi-disciplinary environment.

There is a paucity of data from India, and a majority are retrospective series from tertiary centres. Regimens used in childhood ALL are predominantly western paediatric non-contemporaneous protocols or their modifications, and commonly include MCP-841 and Berlin–Frankfurt–Münster (BFM)-95. Based on the CONCORD statement (global surveillance of trends in cancer survival), the five-year net OS rate in children with ALL in India was estimated to be in the range of 54–75%.[25] A recent review of retrospective data of childhood ALL from various Indian tertiary care centres

reported an OS and EFS in the range 45–81% and 41–70% respectively.[26] In the AYA group, treatment regimens have varied between paediatric-inspired protocols (BFM-based), increased-dosage cyclophosphamide, vincristine (VCR) and daunorubicin (DNR) (hyper-CVAD), or adult protocols (e.g., GMALL). A systematic review of AYA ALL reported the five-year OS rates from different Indian retrospective series to be in the range of 38–58%.[27] Multicentre collaborative efforts are attempting to address several real-world clinical questions encountered by haematologists/oncologists treating ALL of the young in India, and early results are promising.[28,29] Many of these treatments are possible in India due to the availability of generics, and biosimilar preparations of drugs like L-asparaginase (L-ASAP) and rituximab. However, challenges remain.[30,31]

Our institution is a not-for-profit trust-based comprehensive cancer centre located in eastern India, and we are a regional referral institution. Referral pathways for cancer care in most of India are a work-in-progress, and are currently based on geographical access, payment patterns, and treatment experience and reputation of the centres. This is very relevant in the care of the young, with the added dimension of significant emotional challenges associated with a leukaemia diagnosis in the family.[32] Payment patterns in our institution are predominantly out-of-pocket with generous subsidies or financial assistance provided on named-patient basis, by philanthropic initiatives by different non-governmental and government organisations.

Our institution has the full complement of in-house diagnostic and imaging services, as applicable to a tertiary-care comprehensive cancer centre treating haematological and solid-organ cancers. They are compliant with country-specific standards for accreditation and are enrolled in national and international external quality assessment (EQAS) programmes. For this patient, apart from ordering for a complete blood count (CBC), peripheral smear, serum chemistries [including lactate dehydrogenase (LDH)], electrolytes, renal and liver functions, etc., coagulation panel, serology (HIV-1&2, HBsAg, hepatitis core antibody and anti-HCV antibodies), we would request for a BM aspirate and trephine biopsy, and a lumbar puncture (LP) (with IT chemotherapy). Further, we would request BM aspirate immunophenotyping (including ploidy), karyotyping, and FISH-based cytogenetic testing to look for recurrent cytogenetic abnormalities. In addition, the molecular laboratory has the clinical testing facility for PCR-based detection and quantification of entities such as Philadelphia chromosome-positive ($Ph1^{+}$) ALL. The MRD platforms, using FCM and qPCR for *BCR–ABL1*, are used routinely in the management of ALL at our centre. In the research domain, high-throughput sequencing-based approaches are being used in ALL and are occasionally accessed clinically on a case-by-case basis (e.g., Trusight®, New York, NY, USA; myeloid panel for early T-cell precursor ALL). The turnover time(s) are within hours for routine laboratory investigations, while the BM morphology is reported within 72 h for aspirates and five days for biopsy. FCM reports are generally available within 48–72 h, while cytogenetics reports take 7–10 days for karyotyping and 3–5 days for the FISH panel. Routine PCR-based molecular studies, like *BCR–ABL1* reporting, take around 10 working days.

In the rest of India, facilities for comprehensive in-house laboratory testing for malignant disorders are few and far between. In most centres, many of the afore-mentioned tests are outsourced to private laboratories, or to referral institutions across the country. Many laboratories are compliant with country-specific accreditation norms, a few are also compliant with international accreditations and EQAS programmes. However, these cannot be generalised for all labs in the country, and India faces significant challenges on this account.[33] Turnover times vary from days to weeks for outsourced tests and may potentially affect real-world clinical management of patients. This challenge is identified as a felt need in the country and regional hubs for testing are being mooted by the Government and professional organisations.

Q2 Fertility preservation

In our country, most patients present with a heavy disease burden at a late stage and the immediate priority for most haematology/oncology clinicians would be to stabilise the patient and begin cytoreduction at the earliest. A majority of clinicians skip discussions on fertility preservation due to some of the following reasons: lack of patient and physician awareness, lack of time to discuss in a busy clinic, availability of onco-fertility expertise, lack of an organised system for referral, additional costs of care, anticipated delay in initiating cancer-specific treatment, and prioritisation of cancer treatment by patient and family stakeholders.[34–36] At our centre, most clinicians do mention fertility-related issues related to treatment during the counselling process. We do not have an in-house facility for the same. Though sperm cryopreservation facilities are available, expertise in oocyte cryopreservation methods is very limited and cost-intensive in our region. Further, very few patients prioritise this aspect of clinical care due to cost constraints and anticipated delays in initiating cancer treatment.

Q3 Prognostication and induction

This patient, who belongs to the AYA age group (15–40 years), in India is likely to be treated by a paediatric haemato-oncologist, adult haematologist, medical oncologist, or occasionally by clinicians who have undergone brief training periods in cancer care at tertiary centres. This would essentially depend on the geographic location of the centre that the patient reports to. Most referral institutions in the country are now transitioning towards paediatric-inspired protocols for the treatment of ALL in the adolescent and young adult group of patients. A recent systematic review

and large retrospective studies indicate this transition in treatments.[27,37] This has also been facilitated by an increasing crosstalk and collaboration occurring between adult and paediatric haemato-oncology physicians within and outside their respective institutions.

We would first stabilise the patient with standard tumour lysis prophylaxis approach, inclusive but not restricted to hydration, allopurinol and/or rasburicase. We would prognosticate the patient-based established and ongoing paediatric-inspired ALL treatment protocols appropriate for pre-B ALL. She is likely to receive the In POG-ALL-15-01 protocol which is an ongoing multi-centre national clinical trial in India for childhood ALL. She will be stratified in the intermediate risk group based on her age and high total leucocyte count (TLC, $>50 \times 10^9$/l). The protocol includes a corticosteroid pre-phase, and the tyrosine kinase inhibitor (TKI) used in this protocol for BCR–ABL1-positive ALL is imatinib.

With growing experience, our group is increasingly using paediatric-inspired ALL protocols in the AYA age group, up to the age of 40 years. This has occurred over the last 5–6 years, with a clearer understanding of the nuances of delivering more intensive therapy, which includes scheduling of L-ASAP, increased supportive care needs and higher costs of hospitalisations, among others. Availability of a reliable MRD platform, MRD-based treatment stratification, intensive-care support, and greater interaction with the paediatric haematology group have further facilitated this transition. Other paediatric-inspired protocols in common use in India are adaptations from non-contemporaneous western protocols.[37,38] A reduction in relapse and ALL-related mortality has been observed at an incremental cost of treatment-related toxicity. It would be worthwhile to mention here that an early protocol used in India, MCP-841, continues to be used in some centres in India, especially in institutions where cost constraints and logistic challenges of delivering intensive therapies are of significant clinical and administrative concern.[27,39]

Q4 Definition of CR and follow-up

At our institution, post-induction CR (approximately by D35) is defined by all the following: complete recovery from symptoms and physical findings at presentation, haematological CR on PB (± recovery of blood counts) examination, morphological CR on BM examination with adequate cellularity and <5% myeloblasts with no lymphoblasts, absence of blasts in cerebrospinal fluid (CSF), and where appropriate, resolution of testicular involvement/mediastinal mass documented by the modality of imaging, as at diagnosis. MRD monitoring by BM aspirate FCM is undertaken after the induction (in all patients) and consolidation (in most patients) phases of therapy. In Ph^+ ALL, MRD by qPCR is done additionally. Patients with poor prednisolone response, central nervous system (CNS) disease, post-induction MRD-positive status, and HR cytogenetics [*MLL*/*KMT2A* rearranged leukaemia, low hypodiploidy, t(17;19) (q22;p13) (*TCF3–HLF*), intrachromosomal amplification of chromosome 21 (iAMP21) and t(9;22) (q34;q11) (*BCR–ABL1*)] transition to the HR protocol.

Allogeneic haematopoietic cell transplantation (alloHCT) in this setting is offered for patients at higher risk of relapse, owing to HR cytogenetics (low hypodiploidy, *MLL*/*KMT2A* rearranged), persistent MRD status (post-consolidation) or failure of remission induction. In patients with Ph^+ ALL, alloHCT is now offered only when MRD is $>10^{-4}$ post interim maintenance. We use a total body irradiation (TBI)-based myeloablative conditioning regimen and have the requisite expertise in matched related donor and alternative donor transplantations. There is a paucity of data regarding transplant outcomes in ALL in the AYA group from India. The rate of uptake of alloHCT in India is poor owing primarily to cost constraints followed by fear of side-effects. Available retrospective data are suggestive of a one-year EFS of 64·8% in the childhood ALL group, which included teenagers.[40] In the Ph^+ ALL setting in the AYA age group, overall EFS at four years was in the range of 36%.[41] With the formation of the Indian Society of Blood and Marrow transplantation (ISBMT) recently and a registry programme preceding it, we hope to see consolidated alloHCT outcomes in ALL for different age groups soon enough.

Q5 Long-term follow-up

Maintenance therapy in ALL is hospital-based in our centre. On occasions, where patients come from distant geographic locations, and with the ongoing SARS-CoV-2 pandemic, clinicians liaise with local healthcare facilities and use teleconferencing facilities to manage patients. Hospital-based follow-up involves monthly visits for physical examination, blood tests, growth monitoring, clinical disease assessment, drug toxicity management, dose optimisation of 6-mercaptopurine and methotrexate, and other-directed investigations. Post maintenance, the long-term follow-up strategy includes periodic review every three months for the first two years, every six months between the third and fifth years, and annually thereafter. This is the practice in most tertiary-care centres in India. Long-term toxicities and late effects are monitored by clinical evaluation, with a focus on musculo-skeletal challenges in the near term followed by metabolic syndrome, endocrine, and cardiac effects on longer follow-up.

Most patients do not opt for fertility preservation or cannot afford them. In our practice, we advise marriage or conception only after two years of cessation of all maintenance therapy. There are scanty data on long-term toxicities in ALL patients from India. Retrospective single-institutional studies, which used older treatment protocols in multiple cancer sites including ALL, report growth defects in 4·5–23% of patients, neurocognitive defects in 15%, metabolic syndrome in 6% and fertility-related challenges in 24·5% of patients.[42–44] Only

a multi-institutional systematic approach and data collection are likely to address the information deficit in this area.

The perspective from Ireland

Q1 Diagnosis

In Ireland this young adolescent would be seen by her general practitioner in the first instance. Given her non-specific symptoms, namely five-month history of progressive fatigue with associated menstrual irregularities, she most likely would have been seen on a number of occasions in the primary-care setting before being referred to a paediatric hospital for further evaluation.

Although ALL is the most common cancer in individuals from birth to 21 years of age,[45] it is still rare and its clinical presentation is usually of sudden onset, with the majority of patients presenting with a short history of fatigue or spontaneous bleeding. Therefore, it is not surprising that ALL was not considered early in her diagnostic pathway. It should also be remembered that AYA patients have a prolonged diagnostic pathway when compared with children and older adults despite having an increase in primary-care use.[46] The reason for delay is most likely multifactorial involving non-specific symptomatology and low awareness of cancer occurrence in the AYA population by general practitioners and not solely related to late presentation of AYA with cancer to primary care or hospital setting.[46]

This 15-year-old girl would be transferred to the National Children's Cancer Service at Children's Health Ireland (NCCS/CHI), where all children and young adolescents (0–15 years and 364 days) with cancer in Ireland are referred for diagnostic and therapeutic planning.

Her initial blood diagnostic work-up would include full blood count, blood smear, blood immunophenotyping by eight-colour FCM, coagulation screen with fibrinogen, renal–bone–liver biochemistry profile (including LDH and uric acid), and viral serology (CMV, VZV, HSV and EBV) and immunoglobulins. Under general anaesthesia BM aspirate for cytomorphology, FCM, cytogenetic, FISH and single-nucleotide polymorphism (SNP) array together with trephine biopsy for histology and immunohistochemistry would be procured. If the diagnosis of ALL was made on the initial blood work-up, then LP for cerebrospinal fluid (CSF) cell count, cytospin and FCM with instillation of therapeutic IT chemotherapy would be performed at the same time as initial BM examination.

MRD assessment (BM) by qPCR of rearranged immunoglobin/T-cell receptor genes (Ig/TCR) and thiopurine methyltransferase (TMPT) genotyping would be requested.

Prior to commencing chemotherapy, baseline echocardiography, adolescent gynaecology consultation, pregnancy testing, and fertility counselling would be carried out. As the patient is under 16 years old, written informed consent will be required from the parents/legal guardian but she will be asked for her assent.

Q2 Fertility preservation

Ireland currently has no publicly provided fertility preservation programme for children and young adolescents with cancer. While oocyte freezing is available in the private sector, it is on an *ad-hoc* basis. Ovarian tissue cryopreservation in not available at the time of writing.

Presently, a feasibility study to establish a National Programme for Fertility Preservation in children, AYA (0–24 years) across NCCS/CHI and the Merrion Fertility Centre at the National Maternity Hospital (MFC/NMH) is being conducted. The study is funded (2020–2023) by the non-governmental organisation the Irish Cancer Society and it is anticipated that long-term funding for this programme will be allocated through our public health service providers, the Health Service Executive, in the near future.

Q3 Prognostication and induction

Her age (>10 years) places her in NCI HR and she will receive a four-drug induction consisting of dexamethasone, VCR, DNR and PEG-L-ASAP according to the risk-directed UKALLK 2019 Interim Guideline v1/NCRI UK-ALL 2011 (EudraCT number 2010-020924-22, version 7) protocol and will be placed on Regimen B. If she has HR cytogenetics (*KMT2A* gene fusions, low hypodiploid/near haploid, iAMP21 and t(17;19)(q23;p13)/*TCF3–HLF)* or fails to remit at D29 she will receive the same four-drug induction followed by Regimen C augmented consolidation. Further therapy will then be directed by post-consolidation MRD status.

For over four decades, Ireland has entered children and young adolescents into UK evidence-based randomised peer-reviewed ALL trials. All children and young adolescents with ALL in Ireland during the period 2003–2011 were entered into the UK-ALL 2003 protocol (EudraCT number 2007-004013-34) that turned out to be the first randomised clinical trial to show that stratification of treatment by molecular response improves outcome but also that treatment reduction was feasible for patients predicted to have a low risk (LR) of relapse.[47,48]

Later, in 2021, ALLTogether1 [EudraCT number 2018-001795-38—a treatment study protocol of the ALLTogether Consortium (pan-European) for children and young adults (1–45 years of age) with newly diagnosed ALL] will be open for recruiting and NCCS/CHI will act as the trial-coordinating centre for all AYA with ALL across Ireland.

Q4 Definition of CR and follow-up

As MRD monitoring has redefined CR in ALL, stratification by early cytomorphologic response has been abandoned in patients who have an adequate MRD signal at D29 in the current

protocol. She will be further stratified by cytogenetic risk and MRD level at D29 and recovery from consolidation at week 14.

Scenario 1: She will be assigned to MRD LR if her MRD level is <0·005% (cytogenetic intermediate risk—all others) or <0·1% (cytogenetic good risk—*ETV6-RUNX1* and hyperdiploidy) at D29 and will receive consolidation according to Regimen B. No further MRD assessment will be required.

Scenario 2: She will be assigned to MRD risk if her MRD level is ≥0·005% (cytogenetic intermediate risk—all others) or ≥0·1% (cytogenetic good risk) at D29 and will receive augmented BFM consolidation according to Regimen C. Further MRD assessment will be following count recovery from consolidation at week 14. If her MRD level is <0·05% she will continue on Regimen C but if it is >0·05% she would be deemed MRD HR and follow advice for induction failure.

Q5 Long-term follow-up

She will be 17 years old when she has finished maintenance therapy and for the first year thereafter she would be seen every three months in a long-term follow-up clinic at NCCS/CHI. At 18 years of age, she would transition to one of our eight designated adult cancer centres (closest to where she lives) for further long-term follow-up care. However, from 2022 she would transition to one of the dedicated Adolescent Young Adult Cancer Units (16–24 years) currently being developed in accordance with our National Cancer Strategy (2017–2026).

If she wishes to become pregnant, she would be referred for family planning consultation that would be organised by personnel between NCCS/CHI (AYA cancer clinician, AYA oncology nurse) and MFS/NMH (fertility specialist and specialised nurse).

The perspective from Mali

Q1 Diagnosis

Our paediatric oncology centre is located in Gabriel Touré Teaching Hospital, Bamako, in the capital of Mali. It is the only centre in the country taking care of children with cancer.[49] Patients are referred to this centre from the different regions of the country.

The diagnostic tools presently available in our settings include CBC, BM cytology, chest X-ray, liver function tests, renal function tests, viral studies for Epstein–Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), hepatitis B surface antigen (AgHbs). CNS involvement is checked by smear cytology. By contrast, myeloperoxidase staining, immunophenotyping, karyotyping, molecular biology and MRD detection are not available to us.[50]

Q2 Fertility preservation

In Mali, fertility preservation is possible only in a private clinic, and it is not affordable by many of our patients.

Q3 Prognostication and induction

Given that the patient is more than 10 years old and her leukocyte count is more than 50·000, she is deemed to be at HR.

She will be admitted to in our paediatric oncology unit, where treatment is free because she is less than 18 years old. With a diagnosis of ALL, her treatment protocol will be that of the French–African Pediatric Oncology Group (FAPOG; a group of paediatric oncologists from France and French-speaking countries in Africa) for ALL.[51]

The treatment always begins with deworming first and before prednisone by albendazole and then cytoreduction/induction with prednisone or methylprednisolone over one week in association with IT injection of MTX. PB cytology is done at D8 to evaluate blood drop in blasts and to detect any corticosteroid resistance (defined by the presence of more than 1×10^9/l blast-like cells). Subsequently, cytoreduction consists of three injections of DNR (40 mg/m^2), once a week for three weeks, VCR (1·5 mg/m^2/day), one injection per week for four weeks, dexamethasone PO (6 mg/m^2/day) from day 8 to day 22, L-ASAP (10 000 iu/m^2/day) six injections from D22 to D35. In addition, three IT injections of methotrexate are administered on D1, D8 and D15.

Follow-up BM evaluation is done between D35 and D42.

Q4 Definition of CR and follow-up

We define CR as a normal BM at evaluation with normal maturation of the different cell lineages and a percentage of blast cells less than 5% concomitantly with a neutrophil count of more than 1×10^9/l and a platelets count of more than 100×10^9/l.

AlloHCT is not possible in Mali and decision-making about this modality is thus never done at our institution. After the induction phase, all patients therefore proceed straight to intensification treatment. The consolidation phase lasts 50 days with the following drugs: VCR, one injection per week for four weeks (dosage as above), prednisone PO for three weeks 40 mg/m^2, 6-MP PO 25 mg/m^2 for 50 days, four infusions of high-dose MTX (3 g/m^2) and 12 doses of Lederfoline. Four IT injections of MTX for CNS prophylaxis are performed on D2, D16, D30 and D42.

Intensification therapy is comprised of two parts: (i) VCR 1·5 mg/m^2/D1, D8 and D15, three injections of adriamycine between D1 and D15, dexamethasone and two IT injection of MTX on D1 and D29. The second part consists of injection of VCR 1·5 mg/m^2/day on D1, D8, and D15, as well as high-dose cyclophosphamide 2 g/m^2 on D29.

Oral maintenance therapy lasting for two years, consists of 6-MP 50 mg/m^2 daily and MTX 25 mg/m^2 weekly. These are only paused in weeks with IT MTX, of which six were administered monthly during the first six months.

Q5 Long-term follow-up

CBC and liver function will be checked every two months for the first year after maintenance therapy, every three

months for the second and third year and then every year until age 18, when she will be referred to an adult haemato-oncologist at the oncology service of teaching Hospital Point G, Bamako.

If and when she wants to become pregnant, she will be referred to a specialist in gynaecology and obstetrics. However, our centre generally advises patients like her not to become pregnant.

The perspective from Tanzania (P Ewald and P Scanlan)

Q1 Diagnosis

Fifteen years ago, not a single child survived acute leukaemia in Tanzania. These days, of the more than 80 children who are diagnosed annually more than 50% are cured. Care is centralised at Muhimbili National Hospital (MNH) where patients remain as inpatients for the entire intensive phase of their treatment (typically five months). The service is provided free of charge [through a partnership between MNH and Tumaini la Maisha (TLM), a children's cancer charity that supplies all chemotherapy, diagnostics and other supports to every child]. Despite many improvements children tend to present late with advanced disease leading to the sub-optimal survival rates outlined above. A history of five months of symptoms as in the example provided would be a very typical story for a child with ALL in Tanzania.

For every child suspected of acute leukaemia in Tanzania a full blood picture and a peripheral smear are the first investigations performed at all sites. If blasts are visible in the PB smear, a PB sample is sent to MNH for FCM, to confirm the diagnosis. This is offered for free to all children, no matter where in the country they present. Regularly, this is sufficient and a BM test is not required at diagnosis. If the peripheral smear does not confirm blasts or if the PB FCM is negative, but the clinical suspicion for acute leukaemia is high, then a BM FCM test and/or biopsy is also completed. Again, these are processed centrally at MNH. The SEREN genetics lab has recently begun molecular testing and soon will be able to provide genetic analysis for children with ALL (https://www.ox.ac.uk/research/research-impact/seren).

Q2 Fertility preservation

There are no possibilities for this in Tanzania.

Q3 Prognostication and induction

The treatment protocol used in Tanzania is a modified UKALL 2003 protocol. All treatment is given free of charge through a partnership between government, MNH and the charity Tumaini la Maisha (https://www.wearetlm.org, which provides all chemotherapy, as well as a range of other diagnostic and psycho-social support). Treatment from pre-phase to delayed intensification for all children up to the age of 18years is conducted at the national paediatric oncology centre at MNH in Dar es Salaam (although in 2021, two further centres have begun offering care regionally).

The initial prognosis for a child with pre-B ALL is determined using a combination of the child's age, highest pre-treatment white-cell count, ALL cell sub-type, presence of bulky or reservoir disease (CNS or testicular), response to pre-phase corticosteroids, early response to remission induction and finally, and—most importantly—the D28 BM analysis and clinical assessment.

There are a number of modifications regarding investigations and treatment during the diagnostic and remission phase of the treatment. BM is not always done to make the diagnosis, and is then only done on D15 for those few who had a diagnostic marrow. The reason we use PB FCM to confirm the diagnosis as often as possible is due to the fact that the children generally present late with large disease and are often clinically very unstable. No cytochemistry analysis is possible.

CSF analysis is not always possible prior to starting treatment. This is due to the shortage of platelets and the inherent risk of a LP in a child with low platelets and high circulating blast count. The LP is delayed until platelets are available and the blast count drops below 50.

As treatment a pre-phase of prednisolone is given to all children for seven days. As a result, the child only receives three weeks and a tapering fourth week of dexamethasone in the remission induction phase. We introduced this in an attempt to cytoreduce gently in the first week to reduce early mortality due to advanced disease resulting in poorly tolerated chemotherapy, especially when anthracyclines were involved.[52] This was also shown by the BFM group as a very instructive minimally invasive response to treatment assessment tool.

Due to cost, six doses of 10 000 iu/m^2 of L-ASAP are given instead of each prescribed dose of PEG-ASAP. Likewise, triple IT chemotherapy is given instead of MTX monotherapy. The latter is also based on an early study we published showing that children with leukaemia were relapsing at an alarming rate.[53] We introduced a number of measures to address this, and adding triple IT chemotherapy treatment was a very important measure.

All children receive either Regimen B or C, no child receives Regimen A of this protocol. This is based on multiple studies from South Africa that have shown that even when properly risk-stratified and treated accordingly and for free, black children experienced a minimum of 20% worse outcomes than other ethnicities.[54,55]

Tyrosine kinase inhibitors TKIs are not used in ALL treatment. Although there is free access to both first- and second-line TKIs in Tanzania through the MAX Foundation, free testing for the Ph1 chromosome is not currently locally available [for the rare child suspected of chronic myeloid leukaemia (CML), samples are sent to an international partner

lab]. It is not currently feasible to do the same for every child with ALL, meaning that TKIs are not practically available for the treatment of ALL patients.

Q4 Definition of CR and follow-up

Complete remission (CR) is defined as an undetectable MRD in a BM FCM test to a sensitivity of 0·1% on D28 of remission induction. If CR is achieved and the child remains stable and well, no further BM analysis is done unless clinically indicated. If CR has been partially achieved on D28 (less than 5% detectable), we repeat this test at the end of augmented consolidation.

The remainder of our treatment follows exactly the same protocol as the UK-ALL protocol other than the previously mentioned escalated IT therapy and the use of L-ASAP.

Treatment failure is defined as a child who does not achieve sufficient CR (more than 5% blasts detectable) at the end of CR induction or any detectable disease on MRD FCM following consolidation. All these children are moved to palliative care at this point. AlloHCT is not currently available in Tanzania, although that may change in the coming years.

Children who fail to achieve CR are only referred abroad for alloHCT if the family has significant means. Even then we caution against this option unless the child has a matched sibling donor (we can test siblings through a partner in Germany). Of the very few children who travelled without a sibling donor in the past, all were offered only maternal haplotype transplants and each child died abroad in an intensive-care setting.

Q5 Long-term follow-up

Once the intensive phase of their treatment is complete and the child begins maintenance treatment, children are returned to a shared-care site. Most children visit their hospital every 3–4 weeks and maintenance medications are modified in the standard way. Once treatment is complete, all children are reviewed regularly with a clinical exam and a blood count until they are five years post treatment and annually thereafter. No special advice is given to patients regarding fertility. On a number of occasions former patients have happily informed us of the news of becoming proud new Mama's.

The perspective from Thailand

Q1 Diagnosis

Chiang Rai is a province in the north of Thailand and it borders on Myanmar and Laos. Patients from these countries will often come across seeking better health care. Unfortunately, they are not able to access any coverage for diagnosis or treatment and will therefore have to pay for all expenses incurred. In practice, this means that they can afford only laboratory investigations and some supportive care, but rarely any cytoreductive therapy.

In this case, an adolescent female presented with anaemia, leukocytosis and thrombocytopenia. The most likely diagnosis is acute leukaemia that can be either ALL or acute myeloid leukaemia (AML). In Thailand we routinely perform a CBC and evaluate the morphology of immature cells, which is done by the local medical intern. If acute leukaemia is found likely, BM aspirate will be sent for direct morphology examination and, in addition, BM fluid would be collected. BM smear examination would be completed and reported within a few hours and then, if the BM smear suggests leukaemia, the collected BM fluid would be sent for FCM and cytogenetic studies. A haematologist in our centre usually selects one panel of FCM, either AML or ALL, based on morphology of blast cells from the BM smear, to save cost that account for approximately 150€/panel. If ALL is likely, BM fluid will also be sent for *BCR–ABL1* by qPCR technique to detect $Ph1^+$ ALL. An average turnaround time of FCM, cytogenetic study, and qPCR for *BCR–ABL1* is three days, four weeks, and two weeks, respectively. All of these laboratory techniques cannot be done in Chiang Rai, a provincial hospital, at the present time. Consequently, samples are shipped to a private laboratory service in Bangkok. A BM core biopsy is performed at the same time as for immunohistochemical stains, the result of which was reported within 2–4 weeks. In addition, a computed tomography (CT) scan will be performed in case of a clinical suspicion of involvement by leukaemic cells of brain, lymph node, mediastinum, and testis.

Q2 Fertility preservation

When chemotherapy is initiated in adolescents and reproductive-aged patients, fertility preservation is an important concern.[56] In Thailand, the most common method for female fertility preservation is oocyte cryopreservation that has been shown to be successful in adolescents.[57] Unfortunately, ovarian tissue cryopreservation and transplantation that does not delay the induction chemotherapy is uncommon. Thus, in Thailand, fertility preservation is only feasible in a limited number of hospitals in the large cities, where private hospitals and university hospitals are located. Consequently, fertility preservation is not available in Chiang Rai hospital.

Therefore, if the patient in our centre wants to preserve her fertility, she needs to be referred to such centres leading to a longer delay of specific therapy. This issue is very important to explain and discuss with the patient, especially the benefit of fertility preservation and the risk of disease progression and bleeding tendency. In addition, economic issues are also significant since the cost of fertility preservation are at the patient's expense. For most local patients the cost (more than 3000€) far exceeds their economic capabilities. Thus, in practical terms, very few patients will get access

to fertility preservation before chemotherapy. Moreover, given that the risk of operative bleeding in acute leukaemia is relatively higher than other cancers, several patients with the means for the procedure have not undergone the procedure because they choose to avoid delaying chemotherapy.

Q3 Prognostication and induction

In Thailand, the cytoreduction strategies have not markedly changed during the latest decade. However, risk stratification including more molecular criteria and transplantation has become more accessible. Adolescents more than 15 years old are referred to an adult medical centre. The chemotherapy protocol in children is well established as a national protocol for the treatment of childhood cancers by the Thai paediatric oncology group (ThaiPOG). The paediatric protocol is also applied in AYA aged up to 40 years old. The ALL risk stratifications are routinely evaluated by using clinical and optional molecular criteria according to the ThaiPOG protocol. qPCR for the BCR–ABL fusion proteins P190 and P210 is routinely performed for diagnosis of $Ph1^+$ ALL that suggests adding TKI to the paediatric ALL protocol. In this case, the patient is 15 years old, and will be classified into the very (V) HR group. The VHR paediatric-based ALL protocol (ThaiPOG-ALL-13-3) derived from the COG AALL1131[58] will be initiated as soon as possible after a BM FCM report has been received. In Chiang Rai, the patient will get a phase I induction chemotherapy, in this protocol comprised of four drugs: VCR 1.5 mg/m^2/dose IV (D1, D8, D15, D22), prednisolone 30 mg/m^2/dose PO BID (Day 1–28), doxorubicine 25 mg/m^2/dose IV (D1, D8, D15, D22), L-ASAP 10 000 iu/m^2/dose IM (days 4, 6, 8, 10, 12, 14), which constitute the backbone for induction regimen with IT MTX 15 mg (D1, D8, D29). If the Ph1 chromosome is present or if qPCR for *BCR–ABL* is positive, the protocol will proceed to the Ph^+ ALL protocol (ThaiPOG-ALL-1304) as in COG AALL 0031,[59] and the EsPhALL protocol.[60] The available TKIs in Thailand (imatinib, nilotinib, dasatinib) are recommended for combination with chemotherapy. The most readily available TKI for the ALL protocol is imatinib 340 mg/m^2 PO daily on D15–D36 after the first two weeks of the VHR-ALL induction protocol with an average expense of imatinib of 50€/day. However, few patients will gain access to TKI, as only civil servants with a benefit scheme can get this medication as part of their coverage. Thus, for all the patients enrolled in the the general social-security scheme in Thailand such expenses are not covered.

Q4 Definition of CR and follow-up

To evaluate CR status after induction, the BM aspirate smear at D29 of induction is assessed. A BM lymphoblast count of less than 5 percent is defined as CR. In case of prior positivity of qPCR for *BCR–ABL*, this test will be repeated and processed at a private laboratory service in Bangkok. A MRD of 0·01 or more is defined as poor prognosis.[61] This methodology is available in only few centres in Thailand. Thus, MRD is not evaluated in most centres, including our institution. Should the patients want this feature, it will be at their own expense (approximately 160€).

Unfavourable cytogenetics, e.g. the presence of Ph1 chromosome and hypodiploidy (less than 44 chromosomes), are categorised as poor prognosis.[62] Testing for unfavourable molecular features such as iAMP21 and *MLL* rearrangement is also not performed because of unavailability in most hospitals in Thailand. In the present case, if initially she has no BCR–ABL, no t(9;11) (q34;q11), no hypodiploidy, and attains CR after induction, she will proceed to phase II augmented–consolidation, phase III augmented–interim–maintenance-I, phase IV augmented–delay–intensification, phase V interim–maintenance-II and phase VI augmented–maintenance of the ThaiPOG-ALL protocol. In contrast, if post-induction assessment on D29 shows induction failure or initial karyotyping shows hypodiploidy, post-consolidation alloHCT will proceed with any available donor, but in a specialised department in Bangkok. Moreover, in case of $Ph1^+$, the Ph^+ ALL protocol (ThaiPOG-ALL-1304) will be initiated with the possibility of alloHCT after chemotherapy phase IV interim–maintenance-I.

Q5 Long-term follow-up

Given that the patient is in CR, end-of-therapy evaluation will be done, including BM aspiration and biopsy, echocardiography, electrocardiogram and blood chemistry, typically six months after diagnosis. The patient will be followed by clinical examination and CBC every 1–2 months in the first year off therapy, every two months in the second year off therapy, every three months in the third year off therapy, every six months in the fourth year off therapy and then yearly lifelong. With respect to reproduction, chemotherapy toxicity to oocytes has been reported and the patient should avoid becoming pregnant within the first six-month period following chemotherapy.[63] In case of prior fertility cryopreservation, her frozen oocyte or embryo will be fertilised and her fertility restored with the success rate being approximately 20–30%.[64] Although chemotherapy backbone agents in the ALL protocol are not reported to have a high gonadotoxic impact in the patient, a decrease in fertility rate after chemotherapy has been reported even if the menstrual cycles are resumed.[63] At our centre, the adolescent patient and her parents will be informed about the risk and benefit of fertility preservation as well as the expense.

Discussion (A Biondi, V Conter and P Hokland)

The experiences reported here clearly show the complexity of the 'global' management of ALL in childhood or adolescence worldwide, which depends on the economic situation and health system of each country. The term low-income

countries (LIC) is often used to include all non-high-income countries (HIC). There are, however, great differences among the former countries. According to the World Bank classification, Mali is a LIC, while India and Tanzania are LMICs, Brazil and Thailand are upper middle income countries (UMIC), and Ireland is a HIC.[65,66] Of note, large countries such as Brazil or India present also different economic and epidemiological situations within the countries themselves, as explained by Lee, by Ewald and Scanlan and by Chandy and Radhakrishnan. In these countries, there are, in fact, also centres of excellence, as exemplified by as the Tata Medical Center in Kolkata, where most advanced therapies can be delivered. However, in general, the access to these treatments is usually restricted to a minority of patients covered by adequate health insurance or private resources.

Diagnosis of ALL for this 15-year old girl at the CHU Gabriel Touré Bamako Institution, in Mali, would be based only on morphological assessment of BM. This approach is at risk of wrong diagnosis, even for people with great expertise in haematopathology. In this context, it could be suggested to rely on cytochemistry staining for periodic acid-Schiff (PAS), alpha naphthyl acetate esterase (ANAE) and peroxidase. This methodology, regularly used in the 70s, is of very low cost and allows discriminating the major subtypes of leukaemia, and in particular ALL from AML. Furthermore, it should be considered that the alkaline phosphatase/anti-alkaline phosphatase (APAAP) method to stain PB films, BM smears, and cytocentrifuge preparations is also a very simple and low-cost technology,[67] which was widely used in the 80s to dissect different leukaemia subtypes. In our project of cooperation with the Paediatric Hospital of Managua, which started in the late 80s, both these methodologies were implemented and used successfully.[68,69] Needless to say, this ease of implementation might not apply to the Bamako set-up, but it is encouraging that other studies from this continent have been initiated to institute a graduated-intensity approach.[70]

Of interest, immunophenotyping by FCM is available for patients of all five other hospitals taken into consideration here, in-house or as outsourcing, including private laboratories. As explained by in the contributions from India and Brazil, however, the situation within their countries varies considerably, often depending on economical restrictions, and—though not mentioned—shortage of reagents and delays in equipment maintenance are not uncommon in non-HIC. We thus agree with the suggestion by Lee that simpler and cheap methodologies such as cytochemistry mentioned above should still be available in institutions where these risks exist, to replace FCM when needed. The statement by Chandy that in India "*more sophisticated tests based on cytogenetics or molecular biology, including MRD testing, vary considerably and are strictly dependent on economic resources,*" may indeed apply to the whole world. In this context, it should be remembered that while advanced diagnostic tools may be crucial for the treatment of specific targeted therapies in patients with poor or inadequate treatment response, the fraction of patients who will actually benefit from these treatment strategies remains quite limited, and the impact on overall cure rates will be minor. Although very important and life-saving for some patients, this aspect may thus not be regarded as crucial for treatment of pre-B ALL worldwide.

Fertility preservation is either doable only in private structures or not available at all. As pointed out by some of the authors, this is not a major issue for patients undergoing first-line conventional treatment for ALL. Fertility generally is not impaired in these patients, although this is the case for patients who will be in need of an alloHCT. It is also true that the need for chemotherapy interruption to perform the procedure successfully is another obstacle. However, it emerges clearly from the reports that the public health systems are unable at this time to provide this service in most countries, regardless of the disease and treatment features.

The definition of the upper paediatric age limit in oncology is quite variable, being generally lower in non-HIC compared to HIC, probably due to the different age distribution. While in Ireland patients up to the age of 16 years are treated in a paediatric institution, in the other countries this 15-year-old girl would be treated in an adult ward (possibly not in India), where, however, lately there has been a progressive trend to treat AYA patients with paediatric-oriented protocols.[71] This aspect thus should not substantially change her treatment.

Planned cytoreductive treatments for pre-B ALL in childhood seem similar in all countries. Induction therapy consists of three or four drugs, and subsequent treatment is derived from well-known HIC successful protocols, although in some of them cumulative doses of expensive drugs are reduced and outcomes are variable. It should be considered for this purpose that studies from the 90s, where all patients diagnosed with ALL were included and targeted therapies were not available, allowed to obtain a five-year EFS of about 75% or higher, which remains rather close to results obtained in more recent studies that generally did not include infants or patients with alloHCT ALL.[72–74] Results in non-HIC countries, despite of improvements as reported above, remain definitely less favourable. This may be due in part, as suggested by Lee, to some ethnical specificities such as the frequency of different cytogenetic ALL subtypes[11] or constitutional genetic variability.[75,76] Other unfavourable factors include late presentation with high tumour burden, delayed diagnosis, denial and abandonment, malnutrition, poor supportive treatments and suboptimal care.[23] Of note, as mentioned by Chandy and Radhakrishnan, the majority of patients in non-HIC do not have a healthcare insurance and in many instances diagnostic procedures and treatments may require out-of-pocket expenditure.

However, the major obstacles to successful treatment, particularly in LIC and LMIC, remain poor adherence and compliance to protocol treatment, abandonment of treatment,

shortage of support therapy, including blood products, and of chemotherapeutic drugs, as reported by many groups.[75] At the Institution in Tanzania, where platelets are not regularly available for patients at the diagnosis of leukaemia, the EFS reported in patients treated with a modified UK-ALL 2003 protocol is only 31% at two years from diagnosis, with a curve still dropping.[50]

The definition of response in terms of CR is quite homogeneous among the centres involved in this report, being based on morphological evaluation of the BM at the end of the induction phase, except for Ireland where CR is defined by MRD assessment. There is, however, a marked variability in molecular response assessment and indications for alloHCT, which is not available for patients in the two African centres. The need for alloHCT and its feasibility in countries with limited resources remain quite controversial. In many of these countries there is a more urgent need to treat much more common haematological diseases, such as sickle-cell disease or thalassaemia. AlloHCT in patients with leukaemia does present additional hurdles due to the need to eradicate the malignant disease. Requirements for this procedure include important support therapy and capability for long-term follow-up and management of sequelae, which may be hard to face in LIC and many LMIC. AlloHCT should, however, be feasible in some LMIC and generally in UMIC if there is a strong local commitment. This is a field where international cooperation can play an essential role.[15]

Follow-up of patients cured of ALL is most important to document sequelae and facilitate early interventions. In the case of this 15-year old girl, for example, there is a relevant risk for avascular necrosis. It is clear from the reports that attention to long-term follow-up is given in all centres, although the quality may be limited by the shortage of resources.

Overall, the reports above show that there is an enormous gap in the treatment of pre-B ALL between HIC and countries with limited resources, with the very important consideration that in LIC many children may die of ALL without coming into contact with the respective healthcare systems. This inequality gap is most striking because it concerns children with a highly curable cancer.

In this frame it is encouraging to observe that, although at different levels, the overall management of paediatric oncology has been steadily improving in the non-HIC described here over the last years. This process needs to be progressively implemented worldwide with local resources and international collaboration, facing step by step the most crucial issues, which may vary depending on the regional situation. To start, the prompt access to oncological centres should be facilitated for children with symptoms suspicious of cancer. Information campaigns may be useful for this purpose. Then, there is a clear need to guarantee at least basic diagnostics, aiming to establish the correct immunophenotype, by FCM if feasible; this requires training technicians and moderate resources. More advanced diagnostic tools, including simplified FCM MRD may follow. Supportive care with drug availability requires adequate resources, which depend heavily on the local economic situation and governmental policies. There is also a strong need for highly qualified medical and nurse staff to pursue treatment compliance and adherence.

There are now many examples of international collaboration which have permitted gradual effective development of successful paediatric oncology in many geographical areas. Methodologies applied have been variable. In the 80s and 90s the most common approach was based on outreach and twinning programmes, where HIC centres were hosting and training people from non-HIC countries and providing direct support to their centres.[67,77,78] In the last decade there has been also a more comprehensive (global) approach, aiming at the development of paediatric oncology in large regions, with more advanced centres which may serve also as hubs for certified medical training and centralised diagnostics.[64,74,77] In this context the conduction of common clinical trials and biological research too may become feasible, providing information which may be useful for the treatment of children in HIC too.[15,16,74,79,80]

Of note, the WHO has recently launched an initiative to reduce the gap between HIC and non-HIC for six malignant diseases in childhood (i.e. ALL, Burkitt lymphoma, Hodgkin lymphoma, retinoblastoma, Wilms tumour, low-grade glioma) for which high cure rates can be obtained.[80] To pursue this goal WHO is also updating the list of essential medical products for paediatric cancer. The commitment of WHO to reduce the gap between HIC and LIC in the field of paediatric oncology constitutes a major step to promote awareness, international cooperation, and progressive involvement of all stakeholders. We are confident that in this context a marked improvement of 'global' paediatric oncology in the current decade will be achieved, reducing significantly the gap between countries with different levels of resources.

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Conflict of interest

None of the authors have any conflicts of interest to declare.

Author contributions

PH devised the concept and wrote the case story. The authors from the different countries wrote their contributions separately. PH collected and edited the contributions.

AB, VC and PH reviewed these and wrote the concluding remarks. PH finalised the manuscript. All authors approved the final version.

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