germline genomes are currently being done by some centres in North America and Europe, to identify new biomarkers and therapeutic targets and to guide the selection of agents for individual patients.[32,33] Similar research studies are beginning to be undertaken in some advanced centres in Asia.

Risk assignment

Risk-directed treatment is the cornerstone of contemporary protocols for acute lymphoblastic leukaemia in countries with enhanced or maximum resources.[4] However, in regions with basic resources, intensification of treatment is not a feasible strategy despite availability of some useful prognostic markers—eg, age, presenting leucocyte count, and early treatment response as assessed by peripheral-blood blast-cell count (panel 2). When resources are limited, risk assignment can be based on these clinical features and, if available, biological features such as immunophenotype and genotype of leukaemia cell, which have prognostic and therapeutic implications. With enhanced resources, additional molecular and cytogenetic features can be assessed to increase precision of risk assessment and, thus, tailor treatment intensity (panel 2).[34] Screening for the oncogene fusion transcript *BCR-ABL1* is recommended in adult patients with acute lymphoblastic leukaemia, not only because it has high incidence and poor prognosis in this age-group but also because ABL tyrosine kinase inhibitors are available for treatment.[5,29]

Quantification of minimal residual disease by allele-specific oligonucleotide PCR (ASO-PCR), amplification of immunoglobulin and T-cell receptor genes, or multiparametric flow cytometry of aberrant surface antigen expression allows accurate submicroscopic measurements of early treatment response, currently the most powerful of all prognostic markers.[4,14,35] Centralised referral laboratories to measure minimal residual disease are recommended for countries with maximum resources. For regions or countries with enhanced or limited resources, a simplified and inexpensive flow cytometric assay of bone-marrow cells—based on the exquisite sensitivity of haematogones to glucocorticoids—can identify patients who have a good treatment response during remission induction and who might benefit from a reduction in treatment.[36] ASO-PCR is a time-consuming and laborious procedure, and the flow cytometric method needs a high level of expertise for meaningful data interpretation; moreover, both assays have limited capacity to monitor clonal evolution during treatment, which introduces the potential for false-negative results. New deep-sequencing methods that can detect very low levels of leukaemia (<0·001%) with prognostic importance[37] will soon become available to centres with maximum resources, and these are expected to overcome the limitations of current approaches for assessment of minimal residual disease.

***Panel 2:* Recommendations for risk assignment, according to resource availability**

Basic resources

Children and adults

- Age
- Leucocyte count
- Day 8 peripheral-blood response

Limited resources

Children

- Age
- Leucocyte count
- Immunophenotype (T cell *vs* B cell)
- Blast-cell count in peripheral blood after 1 week of prednisone treatment, or percentage of leukaemic blast cells in bone marrow at day 8
- Day 15 and end-of-induction bone-marrow response
- If available, RT-PCR of *BCR-ABL1*, *MLL-AFF1*, and *ETV6-RUNX1*

Adults

- Age
- Leucocyte count
- Immunophenotype (T cell *vs* B cell)
- Blast-cell count in peripheral blood after 1 week of prednisone treatment, or percentage of leukaemic blast cells in bone marrow at day 8
- End-of-induction bone-marrow response
- If available, RT-PCR of *BCR-ABL1*
- Cytogenetics for Philadelphia chromosome or fluorescence in-situ hybridisation of *BCR-ABL1*

Enhanced resources

Same as limited, plus

Children

- Optional DNA index
- RT-PCR for *BCR-ABL1*, *MLL-AFF1*, *ETV6-RUNX1*, and *TCF3-PBX1*
- Cytogenetics for hyperdiploidy >50 and hypodiploidy <44
- Fluorescence in-situ hybridisation of chromosomes 4, 10, and 17, and *BCR-ABL1*

Adults

- RT-PCR of *BCR-ABL1* and *MLL-AFF1*
- Cytogenetics for hyperdiploidy >50
- Fluorescence in-situ hybridisation of *BCR-ABL1*
- HLA typing

Maximum resources

Same as enhanced, plus

Children

- Minimal residual disease measurements by IgH or T-cell receptor rearrangements, flow cytometry, or deep sequencing
- Genome-wide analysis to identify lesions responsive to ABL tyrosine kinase inhibitors
- Pharmacogenetics

Adults

- Minimal residual disease measurements by IgH or T-cell receptor rearrangements, flow cytometry, or deep sequencing
- ABL kinase domain mutation analysis, especially for Thr315Ile mutation for selection of alternative tyrosine kinase inhibitors
- Pharmacogenetics

With the advent of genome-wide analyses, almost all cases of acute lymphoblastic leukaemia can be classified genetically.[4,32] Many individuals with Philadelphia chromosome-like (or *BCR-ABL1*-like) leukaemia had genetic abnormalities that predicted responsiveness to ABL tyrosine kinase inhibitors (eg, *NUP214-ABL1*, *EBF1-PDGFRB*) or to JAK inhibitors (eg, *BCR-JAK2*, mutated *IL7R*).[38] These tests should soon be available to Asian centres with maximum resources. Host pharmacogenetics can also affect treatment response. The classic example is the relation between inherited polymorphisms in the gene encoding thiopurine methyltransferase (*TPMT*) and the response to mercaptopurine. Patients who inherit one or two variant alleles that encode either unstable or non-functional TPMT proteins have an increased risk of haemopoietic toxic effects and development of treatment-related leukaemia; therefore, the dose of mercaptopurine must be reduced.[39] However, *TPMT* mutations are rare in Asian populations (about 2–3%) compared with white populations (about 10%),[14] a finding that cannot account for the reduced tolerance of Asian people to mercaptopurine. Further study is needed to ascertain whether polymorphisms of genes encoding enzymes entailed in folate metabolism, or perhaps other genes, affect the response to anti-metabolites in Asian populations.

Panel 3: Proposed protocol for children and adults with acute lymphoblastic leukaemia in countries with basic resources (not risk-stratified)

Induction (two-drug), for 1 month
- Vincristine 1·5 mg/m² per dose*, days 1, 8, 15, and 22
- Prednisolone 40–60 mg/m² per day, for 28 days
- Asparaginase (if available) 6000 U/m² per dose, days 4, 6, 8, 11, 13, and 15
- Intrathecal methotrexate, days 8, 15, and 22

Interim maintenance (part 1), for 8 weeks
- Mercaptopurine 37·5–50 mg/m² or tioguanine 30–40 mg/m²† per night (before bedtime)
- Oral methotrexate 15–20 mg/m² per dose, weeks 2, 4, 6, and 8
- Intrathecal methotrexate, weeks 1, 3, 5, and 7

Delayed intensification (part 1), for 4 weeks
- Vincristine 1·5 mg/m² per dose*, days 1, 8, 15, and 22
- Dexamethasone 4–6 mg/m² per day, for 28 days
- Intrathecal methotrexate, days 1 and 15

Interim maintenance (part 2), for 8 weeks
- Same as interim maintenance part 1

Delayed intensification (part 2), for 4 weeks
- Same as delayed intensification part 1

Maintenance, 4-week block, repeated until 2 years
- Mercaptopurine 37·5–50 mg/m² or tioguanine 30–40 mg/m²† per night, for 28 days
- Oral methotrexate 15–20 mg/m² per week, for 4 weeks
- Dexamethasone 4–6 mg/m² per day, for 5 days during week 3
- Vincristine 1·5 mg/m² per dose*, week 3

*Maximum dose of vincristine should be capped at 2 mg. †Prolonged treatment with tioguanine can be associated with veno-occlusive disease of the liver and thrombocytopenia and should only be used when mercaptopurine is not available.

Treatment of children

Basic resources

In countries with basic resources, family doctors with no formal training in administration of chemotherapy might be responsible for management of patients with cancer. Because drugs and supportive care are limited, our recommended treatment protocol (panel 3) incorporates agents that are available in the WHO list of essential medicines and are minimally myelosuppressive.

We propose a two-drug remission induction regimen with prednisolone and vincristine. Intrathecal methotrexate is recommended to prevent or treat CNS leukaemia, but the first dose can be delayed for up to a week to avoid excessive toxic effects attributable to delayed clearance of methotrexate in patients with renal impairment at diagnosis and to reduce the risk of traumatic lumbar puncture with blast cells, which can adversely affect treatment outcome.[40] On entering complete remission, patients should receive interim maintenance for 8 weeks with oral mercaptopurine or tioguanine (if mercaptopurine is unavailable) every night and methotrexate given every week, alternating oral and intrathecal administration. Delayed intensification with dexamethasone, vincristine, and intrathecal methotrexate is recommended in two parts, interrupted by a second interim maintenance phase, followed by a maintenance phase, to complete a total treatment duration of 2 years.

Although some findings show that one delayed intensification course is enough for patients with a rapid early response to treatment,[41–43] the treatment used in those studies was more intensive than that in our proposed protocol. In a Children's Cancer Group study,[44] double delayed intensification in an overall non-intensive treatment protocol improved the outcome of patients with intermediate-risk acute lymphoblastic leukaemia. Our proposed protocol is low-intensity, non-myelosuppressive, and repetitive, with little interruption. The repetitive blocks simplify training for doctors and nurses on how to administer treatment. About 50–70% of patients might go into remission and 20% might be cured with the two-drug induction followed by maintenance therapy, on the basis of data for treatment regimens used in the USA in the 1960s.[45] Compared with a three-drug or four-drug induction strategy, use of two drugs entails fewer toxic effects and needs less supportive care, which is generally limited in countries with basic resources, thus reducing abandonment rates. However, if asparaginase is affordable, it could be added for 2–3 weeks during remission induction because it is relatively non-myelosuppressive compared with other drugs and might boost long-term survival to 30–50%, according to results of the Children's Cancer Group series of studies.[46]

Limited resources

In countries with limited resources, efforts to train and certify oncologists and nurses are helpful to establish a team of trained clinicians. A programme whereby an institution in a developed country is paired with an organisation in a country with limited resources could facilitate development of effective cancer-treatment programmes.[47,48] Internet-based communication initiatives such as Cure4Kids are invaluable for training of teams and management of difficult cases.

We recommend a three-drug induction protocol for all paediatric patients (panel 4), with added daunorubicin and extended asparaginase treatment for children with a poor early response (based on assessment of peripheral blood at day 8 or bone marrow at day 15). Protocols developed by the US Children's Oncology Group that feature a three-drug induction regimen (dexamethasone, asparaginase, and vincristine, without anthracyclines), a 4-week low-intensity consolidation phase, and no high-dose methotrexate have yielded good results, particularly for children with standard-risk B-cell acute lymphoblastic leukaemia.[28] In a low-income province of Indonesia, three-drug induction with only two doses of asparaginase induced 71% complete remission; failures included abandonment in 12% of patients, toxic deaths in 10%, and resistant disease in 7%.[49] Risk stratification is possible and desirable. For consolidation treatment in children with high-risk disease, we propose use of a higher dose of cyclophosphamide than for those with standard-risk disease, because this drug improves outcome particularly for patients with T-cell acute lymphoblastic leukaemia.[50] In cases of high-risk acute lymphoblastic leukaemia, intermediate-dose methotrexate (1 g/m² infusion over 24 h with folinic acid rescue at 10 mg/m², starting at 42 h and repeated every

For more on Cure4Kids see http://www.cure4kids.org

Panel 4: **Proposed protocol for children with acute lymphoblastic leukaemia in countries with limited resources**

Induction (three-drug, risk stratified), for 1 month
- Prednisolone 40–60 mg/m² per day, for 28 days (standard-risk disease)
- Dexamethasone 6 mg/m² per day, for 28 days (high-risk disease)
- Vincristine 1·5 mg/m² per dose*, days 1, 8, 15, and 22
- Asparaginase 6000 U/m² per dose, days 4, 6, 8, 11, 13, and 15
- Daunorubicin 30 mg/m², day 15, and asparaginase 6000 U/m², days 18, 20, and 22, can be added for poor early-responders
- Intrathecal methotrexate, days 8, 15, and 22

Consolidation, for 3–4 weeks
- Intravenous cyclophosphamide 250 mg/m², day 1 (standard-risk disease)
- Intravenous cyclophosphamide 500 mg/m², day 1 (high-risk disease)
- Subcutaneous cytarabine 75 mg/m² per day, for 4 days
- Mercaptopurine 37·5–50 mg/m² or tioguanine 30–40 mg/m²† per night, for 14 days
- Intrathecal methotrexate, days 1 and 15

Interim treatment (part 1; after recovery from consolidation), for 8 weeks
- Mercaptopurine 37·5–50 mg/m² or tioguanine 30–40 mg/m²† per night
- Oral methotrexate 15–20 mg/m², weeks 2 and 4–8
- Intrathecal methotrexate, weeks 1 and 3

Delayed intensification (part 1), for 4 weeks
- Vincristine 1·5 mg/m² per dose*, days 1, 8, 15, and 22
- Dexamethasone 6 mg/m² per day, for 28 days
- Asparaginase 10 000 U/m² per dose, days 3, 6, 9, 12, 15, and 18 (standard-risk disease)
- Asparaginase 10 000 U/m² per dose, days 3, 6, 9, 12, 15, 18, 21, and 24 (high-risk disease)
- Intrathecal methotrexate, days 1 and 15

Additional treatment (high-risk disease only), for 4 weeks
- Intravenous cyclophosphamide 500 mg/m², day 1
- Subcutaneous cytarabine 75 mg/m² per day, for 4 days
- Mercaptopurine 37·5–50 mg/m² or tioguanine 30–40 mg/m²† per night, for 28 days
- Intrathecal methotrexate, days 1 and 15

Interim treatment (part 2), for 8 weeks
- Mercaptopurine 37·5–50 mg/m² or tioguanine 30–40 mg/m²† per night
- Oral methotrexate 15–20 mg/m², weeks 2–8
- Intrathecal methotrexate, week 1

Delayed intensification (part 2; high-risk disease only), for 4 weeks
- Vincristine 1·5 mg/m² per dose*, days 1, 8, 15, and 22
- Dexamethasone 6 mg/m² per day, for 28 days
- Asparaginase 10 000 U/m² per dose, days 3, 6, 9, 12, 15, 18, 21, and 24
- Intrathecal methotrexate, days 1 and 15

Additional treatment (high-risk disease only), for 4 weeks
- Intravenous cyclophosphamide 500 mg/m², day 1
- Subcutaneous cytarabine 75 mg/m² per day, for 4 days
- Mercaptopurine 37·5–50 mg/m² or tioguanine 30–40 mg/m²† per night
- Intrathecal methotrexate, days 1 and 15

Maintenance, 4-week block, repeated until 2 years
- Mercaptopurine 37·5–50 mg/m² or tioguanine 30–40 mg/m²† per night, for 28 days
- Oral methotrexate 15–20 mg/m² per week, for 4 weeks
- Dexamethasone 4 mg/m² per day, for 5 days during week 3
- Vincristine 1·5 mg/m² per dose*, week 3

*Maximum dose of vincristine should be capped at 2 mg. †Prolonged treatment with tioguanine can be associated with veno-occlusive disease of the liver and thrombocytopenia and should only be used when mercaptopurine is not available.

6 h for three doses) can also be added as part of consolidation, with increased folinic acid rescue implemented on the basis of a raised concentration in serum of creatinine. Dexamethasone is used for post-remission treatment to augment systemic and CNS leukaemia control.[51] Triple intrathecal therapy is recommended for children with T-cell acute lymphoblastic leukaemia and those with leukaemic blast cells in cerebrospinal fluid.[40] On the basis of results from India, in which a similar treatment protocol was used,[52,53] up to 60% of paediatric patients might be cured with this approach. We do not recommend routine prophylactic cranial irradiation because this modality is associated with serious complications and has not been shown convincingly to increase long-term survival in the context of effective systemic and intrathecal treatment, particularly for children with B-cell acute lymphoblastic leukaemia.[4]

Panel 5: **Proposed protocol for children with acute lymphoblastic leukaemia in countries with enhanced or maximum resources**

Induction (three-drug or four-drug, risk-stratified), for 1 month
- Prednisolone 40–60 mg/m² per day, or dexamethasone 6 mg/m² per day, for 28 days
- Vincristine 1·5 mg/m² per dose*, days 1, 8, 15, and 22
- Asparaginase 6000–10 000 U/m² per dose, days 4, 6, 8, 11, 13, and 15, or pegylated asparaginase 1000 U/m², day 3 or 4
- Daunorubicin 25 mg/m², days 1 and 8 (for high-risk disease)
- Asparaginase 10 000 U/m², days 18, 20, and 22, or pegylated asparaginase 1000 U/m², day 15, can be added for high-risk disease or poor early-responders
- Intrathecal methotrexate, days 1 and 15, and days 8 and 22 for patients at increased risk of CNS relapse

Consolidation (part 1), for 3–4 weeks
- Intrathecal cyclophosphamide 1000 mg/m², day 1
- Intrathecal cytarabine 75 mg/m², days 1–4 and 8–11
- Mercaptopurine 50–60 mg/m² per night, days 1–14
- Intrathecal methotrexate, day 1

Consolidation (part 2), for 8 weeks
- High-dose methotrexate 1–2·5 g/m² (low-risk disease) and 5 g/m² (high-risk disease), days 1, 15, 29, and 43
- Mercaptopurine 25 mg/m² per night, days 1–56
- Intrathecal methotrexate, days 1, 15, 29, and 43

Delayed intensification and maintenance, for 2–2·5 years

Treatment according to one of the following protocols:
- Japanese Childhood Cancer and Leukemia Study Group acute lymphoblastic leukaemia 2000 protocol[32]
- Malaysia-Singapore 2003 protocol[54]
- St Jude Total Therapy Study 15 protocol[35]
- UK Acute Lymphoblastic Leukaemia (UKALL) 2003 protocol[41]
- Berlin-Frankfurt-Münster protocol[54]
- Children's Oncology Group protocol[55]
- Dutch Childhood Oncology Group acute lymphoblastic leukaemia 9 protocol[56]
- Dana-Farber Cancer Institute 00-01 protocol[57]

*Maximum dose of vincristine should be capped at 2 mg.

Enhanced or maximum resources

At centres with enhanced or maximum resources, adoption or modification of one of the many risk-directed protocols developed in Asia, western Europe, or the USA, which have yielded good results, should be possible (panel 5).[12,14,35,41,54–57] In general, these protocols feature early intrathecal treatment, consolidation with high-dose methotrexate for high-risk disease and T-cell acute lymphoblastic leukaemia, a delayed intensification phase with dexamethasone, vincristine and asparaginase, and continuation treatment with mercaptopurine and methotrexate for 2–2·5 years. Although haemopoietic stem-cell transplantation from a matched-related donor is recommended for a small proportion (2–6%) of very high-risk paediatric patients, such as those with T-cell or Philadelphia chromosome-positive acute lymphoblastic leukaemia and a poor early response,[14,35,54] long-term survival is only extended marginally compared with that for children treated with intensive chemotherapy only (eg, from 36% to 45% in Philadelphia chromosome-positive acute lymphoblastic leukaemia).[58] Tyrosine kinase inhibitors, if available, should be used in patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia because it can increase 3-year event-free survival from 35% to 80% without use of transplantation.[59] If tyrosine kinase inhibitors are not available, children with this genotype should be treated with the most intensive arm of chemotherapy and undergo transplantation if response to remission induction treatment is poor.

Treatment of adults

Basic resources

To our knowledge, no reports have been published on treatment of adults with acute lymphoblastic leukaemia in countries with basic resources. Therefore, we recommend a similar approach to that for paediatric patients (panel 3). Drug doses should be tailored to the tolerance levels of adults. Referral to tertiary medical centres with adequate expertise and resources should be considered.

Limited, enhanced, and maximum resources

Most chemotherapy regimens used to treat adults with acute lymphoblastic leukaemia in countries with at least limited resources feature multiagent induction, intensification, consolidation, and maintenance phases, together with CNS prophylaxis using intrathecal chemotherapy, with or without cranial irradiation.[60,61] The protocol from the UK Medical Research Council (MRC) Acute Lymphoblastic Leukaemia trial (UKALL XII) and the regimen consisting of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) are both popular because of encouraging results.[61,62] Haemopoietic stem-cell transplantation is a key component in the overall treatment strategy for most, if not all, transplant-eligible adult patients in countries with enhanced or maximum resources (panel 6).[5,63]

The UKALL XII protocol features a two-phase induction regimen with vincristine, prednisolone, daunorubicin, asparaginase, cyclophosphamide, cytarabine, and mercaptopurine, followed by intensification with high-dose methotrexate and asparaginase.[61] Patients in the MRC international trial were randomly allocated either matched-sibling allogeneic transplantation, autologous transplantation, or consolidation and maintenance chemotherapy. Patients randomly assigned consolidation and maintenance therapy received CNS prophylaxis with intrathecal cytarabine and 24 Gy cranial irradiation. Of 1153 adult patients with Philadelphia chromosome-negative disease, 93% achieved complete remission and 5-year survival was 41%.[61] Of 293 patients with Philadelphia chromosome-positive disease, 83% achieved complete remission and 5-year survival was 25%. Risk factors for poor response included age 35 years or older, high leucocyte count (>30×10^9 cells per L for B-cell acute lymphoblastic leukaemia and >100×10^9 cells per L for T-cell acute lymphoblastic leukaemia), and B-cell lineage. This regimen yielded a comparable outcome in Asian patients: 85% of patients had complete remission and 40% were estimated to survive to 5 years when UKALL XII was used in a Singapore centre.[64]

The hyper-CVAD protocol is a dose-intensive regimen comprising eight cycles of fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine, followed by 2 years of maintenance chemotherapy.[62] Granulocyte colony-stimulating factor is given during the intensive chemotherapy cycles. CNS-directed treatment consists of intrathecal methotrexate and cytarabine only; cranial irradiation is not done. In a single-centre study of 288 patients, overall complete remission was 92% with hyper-CVAD, and 5-year survival was 38%, results that are remarkably similar to those with UKALL XII.[63] Advanced age, poor performance status, and high leucocyte count were associated with a poor outcome. In a retrospective analysis of 53 adult patients with acute lymphoblastic leukaemia at one centre in China, treatment with hyper-CVAD resulted in 74% complete remission and 83% survival at 2 years.[65] We recommend either UKALL XII or hyper-CVAD as initial treatment for adults with acute lymphoblastic leukaemia (panel 6).

In view of the suboptimum outcome with chemotherapy alone for adults with acute lymphoblastic leukaemia, and poor survival after relapse, allogeneic transplantation in first remission has been assessed in countries with enhanced or maximum resources.[62,66–69] In a large prospective trial,[67] allogeneic transplantation, chemotherapy alone, and autologous transplantation were assessed. When comparing patients who received an allogeneic transplant with those who received either autologous transplantation or chemotherapy, adults with Philadelphia chromosome-negative disease and an allogeneic transplant had significantly better 5-year survival (53% *vs* 45%) and fewer relapses than those treated with chemotherapy alone or autologous transplantation. High-risk disease was defined as age older than 35 years, high leucocyte count, or prolonged induction (more than 4 weeks) to achieve complete remission.[67] Allogeneic transplantation in both high-risk and standard-risk groups was associated with fewer relapses compared with the other two treatment methods, but the survival benefit was only significant in the standard-risk group, partly because of increased transplant-related mortality in the high-risk group (particularly in older patients). Survival did not differ between patients who received chemotherapy alone and those undergoing autologous transplantation.[67] Researchers on a Cochrane review analysed 14 relevant clinical trials, and their findings also supported use of matched-sibling donor allogeneic transplantation as the optimum post-remission treatment in acute lymphoblastic leukaemia patients aged 15 years or older.[70] Findings of a meta-analysis showed that matched-sibling donor allogeneic transplantation increased survival, but outcome was only improved in younger patients (age <35 years), and the absolute benefit in survival was about 10%.[71] Based on current evidence, we suggest that matched-sibling donor allogeneic transplantation should be considered for adults with Philadelphia chromosome-negative acute lymphoblastic leukaemia, particularly for patients younger than 35 years (panel 6).

In adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia, allogeneic transplantation (related or unrelated donor) in first remission was recommended because of improvements in 3-year survival to 36–40%.[72] However, in recent years, addition

Panel 6: Proposed protocols for adults with acute lymphoblastic leukaemia in countries with limited, enhanced, and maximum resources

Philadelphia chromosome-negative disease
- UKALL XII protocol or hyper-CVAD chemotherapy regimen
- Allogeneic haemopoietic stem-cell transplantation*

Philadelphia chromosome-positive disease
- UKALL XII protocol or hyper-CVAD chemotherapy regimen
- Allogeneic haemopoietic stem-cell transplantation†
- Tyrosine kinase inhibitor such as imatinib mesylate or dasatinib‡ (for countries with enhanced and maximum resources)

UKALL XII=UK Medical Research Council (MRC) Acute Lymphoblastic Leukaemia XII trial. hyper-CVAD=hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone. *Should be considered for all eligible patients with matched-sibling donors in first complete remission (for countries with enhanced and maximum resources). †Should be considered for all eligible patients with matched related or unrelated donors in first complete remission (for countries with enhanced and maximum resources). ‡Can be given with a chemotherapy regimen or before and after allogeneic transplantation.

of tyrosine kinase inhibitors—eg, imatinib mesylate or dasatinib, a second-generation tyrosine kinase inhibitor that can overcome several imatinib-resistant ABL kinase domain mutations—to frontline chemotherapy significantly increased remission rates to more than 90%, without systemic toxic effects. Moreover, when tyrosine kinase inhibitors were given before and after allogeneic transplantation, disease-free survival rose to 60–75%.[73,74] For patients without a donor for allogeneic transplantation, continuation of chemotherapy with a tyrosine kinase inhibitor is recommended. In adults older than 60 years who were ineligible for transplantation, use of a tyrosine kinase inhibitor as a single agent or combined with standard regimens was well-tolerated and led to an improved outcome.[75,76] Although extended follow-up is needed to ascertain the durability of such approaches, we recommend older patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia, who are precluded from intensive treatments, should receive a tyrosine kinase inhibitor combined with corticosteroids or chemotherapy regimens as tolerated (panel 6). Emergence of resistance to tyrosine kinase inhibitors remains a challenge. Current trials are testing the third-generation tyrosine kinase inhibitor ponatinib, which shows promising activity against various ABL kinase domain mutations, including Thr315Ile.[77]

Supportive care

Timely and effective supportive care is important for successful treatment of acute lymphoblastic leukaemia. However, indiscriminate adoption of high-intensity treatments from developed countries is inappropriate without a commensurate level of supportive care. Overtreatment beyond the limits of supportive-care capabilities can lead to excessive death during induction, and high abandonment rates.[78] Thus, the intensity of treatment must be appropriate for the level of supportive care that is available.

In countries with basic, and even limited, resources, about 30% of patients die during induction, exceeding the total cumulative risk of relapse.[79–81] Deaths from infection and bleeding are most common. In a study from northern India,[81] sepsis and bleeding accounted for 53% and 16% of deaths, respectively, with tumour lysis syndrome contributing to 6%.[81] Adequate hydration and use of allopurinol before commencement of steroids or other chemotherapy agents must be done. Table 3 presents some supportive treatment regimens according to the level of available resources. Hunger and colleagues[82] have outlined step-up treatment protocols that might still be too intensive for countries with basic and limited resources in Asia. The Paediatric Oncology in Developing Countries committee of the International Society of Paediatric Oncology has developed recommendations for supportive care in a low-income setting.[83]

Infection control and nutrition

Prevention of infection by simple means is a cost-effective strategy that can pay large dividends. Preferably, patients receiving chemotherapy should be admitted to a separate ward away from those with infectious diseases. Hand hygiene is especially important to prevent cross-infection. Hand-washing facilities with easy accessibility should be made available in wards, or disinfectant hand gels can be placed at the bedside. WHO has published a simple formula for low-cost handrub.[84] A combination of trimethoprim and sulfamethoxazole is essential to prevent *Pneumocystis jirovecii* pneumonitis. A febrile-neutropenia protocol based on local bacterial sensitivity should be developed so that nurses and junior doctors can initiate treatment without delay.

Malnutrition is common among infants in Asian countries (table 2). According to UNICEF, 17% of children under-5 in east Asia and the Pacific region, and 46% in southeast Asia, are underweight.[85] Malnutrition can develop within days after anticancer treatment in children[86] and could be associated with impaired immunity, decreased tolerance to chemotherapy, increased infection rates, and a resultant decline in overall outcome.[87–90] Paediatric patients with acute lymphoblastic leukaemia receiving chemotherapy might also have intestinal parasitic diseases.[91]

Management of tuberculosis

Tuberculosis is endemic in Asia. The incidence of the disease in children with acute lymphoblastic leukaemia is 10–22 times that of young people from similar backgrounds, and about 50% of patients with active tuberculosis at presentation show reactivation within 5 months after completion of remission induction treatment.[92] The two most common forms of infection are pulmonary and meningeal tuberculosis. Culture and sensitivity testing for multiresistant *Mycobacterium tuberculosis* is important. Initial treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months followed by isoniazid and rifampicin for 4 months is needed. Treatment for miliary tuberculosis is prolonged for 12 months to reduce risk of reactivation. Chemotherapy should not be delayed for an extended time, and antituberculosis drugs can be started simultaneously with chemotherapy. Patients might need more than one course of antituberculosis treatment because reactivation is common. Family members must be screened and treated for tuberculosis. Combination antituberculosis drugs in one pill are available in many Asian countries and can improve treatment adherence. In endemic areas, routine Mantoux testing and chest radiography are recommended for all patients newly diagnosed with acute lymphoblastic leukaemia. A positive Mantoux test (induration >20 mm) will require investigations to isolate *M tuberculosis*. In most countries, analysis of early-morning gastric aspirates or induced sputum,

	Children	Adults
Basic resources		
Antiemetics	Metoclopramide and diphenhydramine, lorazepam, chlorpromazine, dexamethasone	Metoclopramide and diphenhydramine, lorazepam, chlorpromazine, dexamethasone, ondansetron
Analgesics	Paracetamol, codeine, morphine	Paracetamol, codeine, morphine
Antibiotics	Cephalosporins, antipseudomonas semisynthetic penicillins, aminoglycosides, trimethoprim-sulfamethoxazole	Cephalosporins, antipseudomonas semisynthetic penicillins, aminoglycosides, trimethoprim-sulfamethoxazole
Blood products	Whole blood (directed), platelets	Whole blood (directed), platelets
Prevention of tumour lysis	Allopurinol	Allopurinol
Limited resources		
Antiemetics	Metoclopramide and diphenhydramine, lorazepam, chlorpromazine, dexamethasone, ondansetron	Metoclopramide and diphenhydramine, lorazepam, chlorpromazine, dexamethasone, ondansetron or granisetron
Analgesics	Intravenous midazolam and ketamine for painful procedures, codeine, methadone, morphine (multiple formulations)	Paracetamol, codeine, methadone, morphine (multiple formulations)
Antibiotics	Broad-spectrum antibiotics, amphotericin B	Broad-spectrum antibiotics, amphotericin B, azoles
Prophylaxis	Trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii*	Trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii*
Blood products	Packed red-blood cells, platelets	Packed red-blood cells, single-donor platelets
Prevention of tumour lysis	Allopurinol	Allopurinol
Enhanced and maximum resources		
Antiemetics	Ondansetron, granisetron, aprepitant	Ondansetron, granisetron, aprepitant
Analgesics	Central venous catheters, sedation or general anaesthesia for painful procedures, fentanyl and other opioids	Central venous catheters, sedation or general anaesthesia for painful procedures, intravenous morphine, fentanyl
Antibiotics	Broad-spectrum antibiotics, carbapenems, azoles, echinocandins	Broad-spectrum antibiotics, carbepenams, azoles, echinocandins, liposomal amphotericin B
Prophylaxis	Trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii*; lamivudine, entecavir, tenofovir for hepatitis B carriers	Trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii*; aciclovir for herpes simplex, varicella zoster; lamivudine, entecavir, tenofovir for hepatitis B carriers
Blood products	Leucocyte-depleted or irradiated blood components, single-donor platelets	Leucocyte-depleted or irradiated blood components, single-donor platelets, HLA-matched platelets
Nutrition	..	Total parenteral nutrition
Prevention of tumour lysis	Allopurinol with or without rasburicase	Allopurinol with or without rasburicase

Table 3: Recommendations for supportive care for children and adults with acute lymphoblastic leukaemia

using nebulised normal saline for 3 days consecutively, is done to look for acid-fast bacilli, and tuberculosis culture and sensitivity testing is recommended. In countries with maximum resources, bronchoalveolar lavage is also acceptable. Because latent tuberculosis can reactivate during the early months of chemotherapy, prophylactic treatment with rifampicin for at least 6 months is common practice, even without a definite focus for infection or positive culture.

Management of hepatitis B

Of the 400 million carriers of hepatitis B virus in the world, 75% live in Asia. Prevalence of chronic hepatitis B virus infection is high in Asia, with the highest proportion of chronic infection (about 8–20%) occurring in southeast Asia, China, central Asia, and the Middle East. Most infections are acquired by vertical transmission from maternal hepatitis B carriers or in early childhood. Active neonatal hepatitis B vaccination programmes in most Asian countries promise to reduce this heavy burden of chronic hepatitis B carriage in the future. Transfusion-acquired hepatitis B infection still occurs in some countries;[93] revaccination for hepatitis B virus at diagnosis of acute lymphoblastic leukaemia can reduce transfusion-acquired infection. Intensive chemotherapy or transplantation might reactivate chronic hepatitis B infections in carriers and could adversely affect treatment. We recommend routine testing of liver function, HBsAg, anti-HBs, and anti-HBc at diagnosis in countries with enhanced or maximum resources. Presence of HBsAg indicates a chronic carrier state and a need for regular quantitative monitoring of hepatitis B virus DNA titres during treatment. Carriers with high titres of hepatitis B virus DNA or raised amounts of liver enzymes might need antiviral treatment with oral nucleosides or nucleotides such as lamivudine, entecavir, or tenofovir. Entecavir is preferable for patients either with high titres of hepatitis B virus or who have undergone prolonged treatment with lamivudine, because of emerging concern about development of resistance to lamivudine.[94,95] Detection of anti-HBc suggests a history of previous natural infection. Monitoring of hepatitis B virus DNA titres is recommended when lasting, unexplained, raised concentrations of liver enzymes or conjugated hyperbilirubinaemia are noted in patients who are positive for anti-HBc. In countries with basic and limited resources, where antiviral treatment is not

available, routine monitoring for hepatitis B virus immune status is not done. Testing for HBsAg and antibodies against hepatitis C virus in all blood products is important to protect patients.

Transfusion support

In countries with basic or limited resources, safe blood components such as platelets and red-blood cells might not be readily available, and even blood banks might not be open daily. For these countries, family donors are commonly asked to complement the volunteer donor pool. In some places, medical students, doctors, and nurses are a ready pool of blood donors. The blood transfusion infrastructure for thalassaemia major—a common inherited blood disorder in southeast Asia—could help provide additional units of random platelets. Local government has an important role in providing resources to set up blood-bank services that meet safety standards. The processing of whole blood into various components helps the rational supply of packed-red-blood cells and random platelets. Government and other public organisations should work together to raise public awareness about the importance of voluntary blood donation.

Pain control

The WHO guideline on pain control recommends a two-step approach that is effective in about 90% of patients.[96] Mild pain in patients with acute lymphoblastic leukaemia can be managed with oral paracetamol; non-steroidal anti-inflammatory drugs should be avoided because thrombocytopenia is common in individuals with leukaemia. Non-pharmacological approaches such as distraction, controlled breathing, and provision of appropriate anticipatory guidance should always be used concomitantly with pharmacological approaches. For moderate-to-severe pain, opiates are necessary. Morphine is the first-line opioid, but the problems of narcotic abuse, misconceptions about addiction, and administrative restriction unfortunately limit the availability of morphine in many Asian countries. Codeine (a prodrug) is commonly available, but it needs to be converted by cytochrome P450 2D6 (CYP2D6) to active morphine in vivo; some people with poor metabolism do not respond to codeine whereas others with ultra-rapid metabolism are at risk of toxic effects with standard doses.[39] The Asian Oncology Summit guideline on palliative care noted that, in about seven Asian countries, patients with cancer have access to more than 1 mg of morphine per person, which is judged adequate for pain relief.[97] The limited access to morphine in other areas of Asia could soon be lessened, because WHO has made access to this drug a high priority for patients with cancer pain.

Many children in Asian countries do not receive sedation and pain control for bone-marrow aspiration and lumbar puncture because of scarce treatment facilities and monitoring devices. Procedure-related pain can induce substantial short-term and long-term anxiety and psychological sequelae. Local analgesia with EMLA cream (lidocaine and prilocaine) and subcutaneous lidocaine and conscious sedation—such as with intravenous midazolam—should be given before painful procedures. Staff should be trained in safe administration of sedation, from monitoring to resuscitation.[98]

	Children	Adults
Basic resources		
Pain control	Paracetamol, codeine, immediate-release oral morphine, dexamethasone	Paracetamol, codeine, immediate-release oral morphine, dexamethasone
Nausea or vomiting	Metoclopramide and diphenhydramine, lorazepam, chlorpromazine, promethazine, dexamethasone	Metaclopramide, prochloperazine, lorazepam, ondansetron, dexamethasone
Dyspnoea	Codeine, morphine, chlorpromazine, lorazepam	Codeine, morphine, chlorpromazine, lorazepam
Limited resources		
Pain control	Immediate-release oral morphine, neuropathic pain adjuvant (eg, gabapentin)	Paracetamol, codeine, immediate-release oral morphine, dexamethasone, slow-release oral morphine, neuropathic pain adjuvant (eg, amitriptyline)
Nausea or vomiting	Metoclopramide and diphenhydramine, lorazepam, chlorpromazine, promethazine, dexamethasone, ondansetron	Metaclopramide, prochloperazine, lorazepam, ondansetron, dexamethasone, granisetron
Dyspnoea	Oxygen, diazepam, morphine	Oxygen, morphine
Psychosocial support	Parent support groups	Hospice care
Enhanced and maximum resources		
Pain control	Transdermal morphine (eg, fentanyl patch), intravenous or patient-controlled analgesic morphine, palliative chemotherapy, slow-release oral morphine, neuropathic pain adjuvants (eg, gabapentin, carbamazepine)	Transdermal morphine (eg, fentanyl patch), intravenous or patient-controlled analgesic morphine, palliative chemotherapy, slow-release oral morphine, neuropathic pain adjuvants (eg, gabapentin, carbamazepine), methadone, neuropathic pain adjuvants (eg, amitriptyline, gabapentin, carbamazepine)
Nausea or vomiting	Ondansetron or granisetron, dexamethasone	Ondansetron or granisetron, dexamethasone
Dyspnoea	Intravenous or patient-controlled analgesic morphine, diazepam or lorazepam	Intravenous or patient-controlled analgesic morphine, diazepam, or lorazepam
Bleeding and anaemia	Blood products	Blood products
Psychosocial support	Hospice care, bereavement support	Hospice care, bereavement support

Table 4: Recommendations for palliative care for children and adults with acute lymphoblastic leukaemia

Search strategy and selection criteria

We searched Medline and PubMed for articles published in English from 2000 to August, 2013, with the terms "acute lymphoblastic leukemia" and "Asia". Additional information was obtained from abstracts presented at the annual meeting of the American Society of Hematology, from the fifth edition of the American Society of Hematology self-assessment program textbook, and from the websites of the National Cancer Institute's Surveillance, Epidemiology and End Results programme (http://seer.cancer.gov), the UN Economic and Social Commission for Asia and the Pacific (http://www.unescap.org), WHO (http://www.who.int), and UNICEF (http://www.unicef.org).

Antiemetics

Setrons—5-hydroxytryptamine antagonists—are highly effective drugs for prevention of nausea and vomiting in both children and adults with acute lymphoblastic leukaemia, but they represent the second most expensive supportive care after parenteral antibiotics. In general, chemotherapy for acute lymphoblastic leukaemia is not strongly emetogenic. Non-setron antiemetics can be used as alternatives. Intravenous metoclopramide combined with intravenous diphenhydramine, to reduce the risk of oculogyric crisis, are effective in countries with basic resources when patients or their families cannot afford setrons. Lorazepam and chlorpromazine might be helpful in some patients.[99,100] Asian governments should consider subsidisation of generic ondansetron because it is cost effective and increases tolerability of treatment for acute lymphoblastic leukaemia. Patients with ultra-rapid metabolising CYP2D6 variants might not respond to ondansetron, and they may need granisetron.[101]

Psychosocial support and palliative care

Several factors contribute to failure of treatment for acute lymphoblastic leukaemia in low-income countries,[102,103] including abandonment of the paediatric patient's treatment by the family and poor adherence to chemotherapy, because of the high costs of treatment and travel to treatment centres and loss of income of parents or carers. Besides social support to enable patients to complete treatment, an education programme for parents could substantially improve outcome.[104]

Palliative care also has an integral role in management of patients with acute lymphoblastic leukaemia, but it is still a fairly new subspecialty that is in development in many low-income countries.[105] Palliative care is not funded fully by governments of most Asian countries, and provision is inadequate because staff are not well-trained and communities not informed enough, particularly for paediatric care. Integration of palliative care through the primary oncology service, with emphasis on comfort and quality of life, can reduce suffering and abandonment and improve survival rates.[106,107] Indeed, early integration of palliative care with oncology treatment has been touted as the optimum model for high-quality comprehensive care of adults and children with cancer.[108] Table 4 summarises some of the key components of palliative care. Paediatric palliative-care programmes should be started, leaning on the experience and resources of well-established adult palliative-care programmes.

Conclusions

As the Asian economy and regional infrastructure continue to improve, patients with acute lymphoblastic leukaemia in areas with basic or limited resources will gain augmented access to treatment, whereas those in countries or regions with enhanced or maximum resources will have additional options of novel targeted therapies. The management proposed in this Review should be modified on the basis of availability of drugs and resources, the experience of the treatment team, environmental factors, and racial and ethnic differences in drug disposition.

Contributors

All authors contributed equally to this Review, including planning the report, doing the literature search, interpreting data, designing the tables, and writing the manuscript. All authors approved the final submitted version.

Conflicts of interests

C-HP has received honoraria from Jazz Pharmaceuticals for chairing a symposium and for giving lectures. All other authors declare that they have no conflicts of interest.

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