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Management of adult and paediatric acute lymphoblastic leukaemia in Asia: resource-stratified guidelines from the Asian Oncology Summit 2013

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Abstract

The survival rates for both adult and children with acute lymphoblastic leukaemia have improved substantially in recent years with wider use of improved risk-directed therapy and supportive care. In nearly all developed countries, clinical practice guidelines have been formulated by multidisciplinary panels of leukaemia experts, with the goal of providing recommendations on standard treatment approaches based on current evidence. However, those guidelines do not take into account resource limitations in low-income countries, including financial and technical challenges. In Asia, there are huge disparities in economy and infrastructure among the countries, and even among different regions in some large countries. This review summarizes the recommendations developed for Asian countries by a panel of adult and paediatric leukaemia therapists, based on the availability of financial, skill and logistical resources, at a consensus session held as part of the 2013 Asian Oncology Summit in Bangkok, Thailand. The management

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strategies described here are stratified by a four-tier system (basic, limited, enhanced and maximum) based on the resources available to a particular country or region.

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common malignancy diagnosed in patients younger than 15 years, accounting for 26% of all cancers and 78% of leukaemias in this age group, and for approximately 20% of adult acute leukaemias.[1] The incidence of childhood ALL varies substantially across geographic regions and by race and ethnicity, partly because of ancestry-related genetic variations.[2] Environmental factors may also play a role, so that the low incidence of ALL in low-income countries, such as Indonesia, has been attributed to early exposure to infection due to early mixing of children.[3] While there is a wealth of biologic and epidemiologic data on ALL in North America and Europe, comparable information is not available for most countries in Asia, which lack hospital- or population-based registries and adequate diagnostic methods. Based on the population estimate for each of the 51 countries by the United Nations Population Division, and assuming an age-adjusted incidence of 1.25 per 100,000 individuals per year (extrapolated from data published by the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results for Asian/Pacific Islander),[1] we estimate that there are at least 54,000 new cases of ALL in Asia each year.

Successful management of childhood ALL is one of the greatest medical achievements of the modern era with 5-year survival rates approaching and even exceeding 90% in most countries in North America and Western Europe.[4] Indeed, recent adaptation of pediatric treatment regimens has improved the 5-year survival rate to approximately 50% in some adult clinical trials.[5] Most Asian governments do not fund prospective data collection, thus hampering our ability to define the treatment results of ALL in Asian countries. Published data in Asia are mostly on pediatric ALL from countries with enhanced or maximal resources (Table 1).[6–15] Only when the governments or charitable organizations fund long-term, prospective collection of data will we know the unbiased outcome of ALL therapy in Asian countries.

Adoption of a step-up approach to treating ALL, one of the most curable cancers in children and an increasingly curable disease in adults, is highly desirable as Asian countries begin to emerge economically. In this article, we summarize consensus recommendations for the evaluation and management of ALL in Asian countries according to their available resources and economic status. We would stress that the management guidelines for countries with basic or limited resources are based mainly on the experience of using low-intensity treatment, with some modifications, developed in the Western countries during the early treatment era when supportive care was suboptimal because of the lack of well documented and published data from Asia. Further, it is beyond the scope of this article to address strategies to overcome many barriers to the implementation of effective management in low-income or mid-income countries, e.g., education and training of patients, families, community, and health professionals; development of local non-governmental organisations that provide psychosocial and financial support; alliances that

combine government, public and private sectors and medical societies; development of twinning programmes and international collaborations; establishment of strategically located oncology units or regional hospital networks; health insurance; and data collection and locally relevant research, which have been subjected to two excellent reviews in the Journal.[16,17]

Resource-stratified consensus recommendations

With the increasing number of diagnostic and therapeutic options, together with the diverse economics and infrastructures in Asia countries, clinical management guidelines should not only aim to improve cure rates and quality of life, but should also be sensitive to resources and cost. We have therefore developed management guidelines and recommendations on the basis of resource availability, using a four-tier system (basic, limited, enhanced and maximum)[18], as a model. The basic level is required to support the adequate function of any healthcare system; the limited level incorporates some financial means and a modest infrastructure that can be used to promote improvements in outcome; while the enhanced level not only can foster improved outcomes but can also provide therapeutic options for the patient. Although the maximal level can support all of the services required by contemporary ALL management strategies, some costly or less practical services may be assigned a lower priority.

One study showed that the projected 5-year survival rates for pediatric cancer in low-income or mid-income countries were directly proportional to several health indicators, including the per capita gross domestic product, per capita gross national income, number of physicians and nurses, and, most significantly, annual health-care expenditure.[16] Table 2 lists data related to child health in selected Asian countries, as reported by the United Nations Economic and Social Commission for Asia and the Pacific in 2012.[19] We arbitrarily divided the countries into one of the four resource categories defined earlier, using the annual total health-care expenditure per capita as our guide. There are important caveats to this classification. Within some large Asian countries, there are huge disparities in economic status from one region to the other. Indeed, one region may have only basic access to oncology care, while in another the facilities and staff may be world class, enabling maximal care to be provided. Hence, we would stress that Asian providers responsible for managing patients with ALL should adopt the recommendations that best match their available resources.

Diagnosis and classification

Initial diagnosis and classification should be carried out in specialised tertiary centres. In large countries with limited infrastructure where travel to main centres may be difficult, diagnostic bone marrow and blood samples may be transported to referral centres for specialised tests. Initial bone marrow smears should be made on new glass slides and additional samples transported in room temperature within 48 hours in sterile EDTA or heparinised (preservative-free heparin, sodium or lithium heparin) tubes. In countries with basic and limited resources where public diagnostic resources may be rudimentary, certified private laboratories, if available, may provide the service.

Children up to 18 years old with ALL are best managed in paediatric centres instead of adult centres. This is because virtually all retrospective studies have shown that adolescents treated in paediatric centres fare significantly better than those of similar ages treated in adult centres.[20] Factors contributing to this observation include intensive use of non-myelosuppressive agents (asparaginase, glucocorticoids and vincristine) and early administration of intrathecal therapy in paediatric regimens, coupled with better treatment adherence by the patients and the clinicians when the medical care is provided in paediatric centres with a better social support network and parental involvement.[20,21] Moreover, many adolescents with ALL require specialised paediatric supportive care, including paediatric intensive care units and dialysis, and some may have undue psychological stress when they are admitted to an adult ward with mainly elderly patients.

Diagnostic tests

Bone marrow aspiration performed under sterile conditions in the posterior iliac region is recommended for diagnosis because the morphology of leukaemic cells in peripheral blood may differ from that in bone marrow, and as many as 20% of patients with acute leukemia lack circulating blast cells at diagnosis.[22] Sternal aspiration is contraindicated in young children and is only rarely necessary in older adolescents. Bone marrow smears stained with May-Grünwald-Giemsa or Wright-Giemsa should be examined by light microscopy (Table 3). If flow cytometry is not available, cytochemistry for myeloperoxidase and nonspecific esterase should be performed to exclude acute myeloid leukaemia. However, cytochemical staining is relatively expensive, so that in countries with basic or limited resources, batched weekly cytochemical staining is acceptable and is included as an addendum report. Indeed, in countries with basic resources, cytochemistry is often the only means by which the diagnosis of ALL can be made. TALL is suspected if a superior mediastinal mass is seen on chest X-ray at diagnosis.

At centres where samples are couriered to central laboratories for cytochemical staining or flow cytometry, treatment can be started on the basis of findings in the initial peripheral blood or bone marrow smear, especially if the patient has hyperleukocytosis or a mediastinal mass. In such cases, remission induction therapy should be non-intensive, starting with one or two drugs only (e.g., prednisolone with or without vincristine). While infants with ALL usually present with a high leukocyte count, special care must be taken in diagnosing those with low leukocyte counts, whose immature atypical lymphocytes can mimic lymphoblasts. In countries with basic and limited resources, delaying treatment in infants with low presenting leukocyte counts until the bone marrow examination is completed may be preferable.

Flow cytometry

The leukemic cell immunophenotype is necessary for accurate diagnosis and risk-directed therapy.[23] Without it, ALL may be misdiagnosed as acute myeloid leukemia or vice versa in approximately 10% of the cases,[24] and some cases with hematogones in regenerating bone marrow after severe infection may be misdiagnosed as leukemia. Immunophenotyping by flow cytometry based on two or three flurochromes is widely available. For countries with limited resources, we recommend a minimum panel of markers for ALL that includes CD19

plus CD22 or cytoplasmic CD79a for B-ALL, CD7 and cytoplasmic CD3 for T-ALL, and myeloperoxidase to exclude acute myeloid leukaemia.[23] These analyses should be performed by experienced laboratory workers. If trained technicians are lacking, the flow cytometry plots can be remotely reviewed by experts using a web-based system.[24,25] Besides CD19 and CD22, CD20 could also be measured in countries with enhanced or maximal resources because monoclonal and bispecific antibodies against these antigens are available for high-risk or refractory cases.[5]

Cytogenetic and molecular genetic analyses

Molecular genetic abnormalities and the cytogenetic features of leukemic cells are highly prognostic of treatment outcome, permitting more precise risk assignment to avoid over- or undertreatment of individual patients.[26] The detection of genetic alterations by cytogenetic techniques (karyotyping and fluorescence in situ hydridization [FISH]) and molecular analyses, including reverse transcription-polymerase chain reaction (PCR) for common oncogene fusion transcripts with prognostic or therapeutic implications, are recommended for countries with at least limited resources.

When resources are limited, molecular screening for oncogene fusion transcripts is preferable to standard karyotyping. Thermocyclers required for PCR analysis are available in many academic institutions. Tertiary centres can partner with their academic institutions to screen for common, prognostically important oncogene fusion transcripts (Table 3). Care must be taken in such studies to avoid cross-contamination by using replicates, positive and negative controls as well as housekeeping genes, such as *GUS* or *ABL1*, to ensure that no mRNA is degraded. By contrast, lymphoblasts grow and band poorly in cytogenetic cultures, and each karyotype must be analyzed manually by trained technicians making it difficult to deliver timely cytogenetic results in busy, poorly staffed centres. Even large cooperative groups, such as the Italian and US Children's Oncology Groups, depend on a combination of molecular oncogene fusion screening, flow cytometric determination of DNA content and FISH for genetic subgrouping in lieu of or in addition to cytogenetics. [27,28] Indeed, molecular and cytogenetic analyses can be successfully carried out in some centers in China that possess an enhanced level of resources.[6,29,30] Studies suggest that frequencies of the t(9;22)(q34;q11) with *BCR-ABL1* fusion and of *HOX11* expression in T-cell ALL are higher, and those of the t(12;21)(p13;q22) with *ETV6-RUNX1* fusion and of hyperdiploidy>50, both favorable genetic subtypes, are lower in Chinese pediatric patients as compared to Western cohorts.[29,31]

With the advent of genome-wide analysis and decreasing cost, large-scale whole exome and whole genome sequencing studies of entire cancer and germline genomes are currently being performed by some centers in North America and Europe to identify new biomarkers and therapeutic targets, and to guide the selection of agents for individual patients (as discussed later).[32,33] Similar research studies are beginning to be carried out in some advanced centers in Asia.

Risk assignment depending on resource availability

Risk-directed treatment is the cornerstone of contemporary ALL protocols in countries with enhanced or maximal resources,[4] but not in those with basic resources, where intensification of therapy is not a feasible strategy despite the availability of some useful prognostic markers, such as age, presenting leukocyte count, and early treatment response as assessed by peripheral blood blast cell count (Table 4). When resources are merely limited, risk assignment can be based on these clinical features and, if available, biologic features (leukemic cell immunophenotype and genotype with prognostic or therapeutic implications) as well. With the availability of enhanced resources, additional molecular and cytogenetics features can be evaluated to increase the precision of risk assessment and thus tailoring of treatment intensity (Table 4), as successfully implemented in the ALL-Inter Continental BFM 2002 study for childhood ALL.[34] Screening for *BCR-ABL1*-positive ALL is strongly recommended in adult patients, not only because of its high incidence and poor prognosis in this age group but also because of the availability of ABL1 tyrosine kinase inhibitors.[5,29]

Minimal residual disease quantification using allele-specific oligonucleotide polymerase chain reaction (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 maximal resources. For regions or countries with enhanced or even limited resources, a simplified and inexpensive flow cytometric assay of bone marrow cells, based on the property of exquisite sensitivity of hematogones to glucocorticoids, can reliably identify patients who have an excellent treatment response during remission induction and may benefit from reduction of therapy.[36] Whereas ASO-PCR amplification is time consuming and laborious, the flow cytometric method requires a high level of expertise for meaningful data interpretation, with both assays having a limited capacity to monitor clonal evolution during treatment, which introduces the potential pitfall of false-negative results. New deep-sequencing methods, which can detect very low levels of leukemia (below 0.01%) with prognostic significance,[37] will soon become available to centers with maximal resources, and are expected to overcome the limitations of current approaches to minimal residual disease assessment.

With the advent of genome-wide analyses, virtually all ALL cases can be classified genetically,[4,32] and many Philadelphia chromosome (Ph)-like (or *BCR-ABL1*-like) ALL cases were found to have genetic abnormalities that predict responsiveness to ABL tyrosine kinase inhibitors (e.g., *NUP214-ABL1*, *EBF1-PDGFRB*) or to JAK inhibitors (e.g., *BCR-JAK2*, mutated *IL7R*).[38] These tests should soon be available to Asian centers with maximal 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 unstable and/or nonfunctional TPMT proteins have an increased risk of hematopoietic toxicity and the development of therapy-related leukemia, and therefore require a reduction of the mercaptopurine dose.[39] However, TPMT mutations are rare among Asians (~2–3%) compared to Caucasians (~10%),[14] a finding that cannot

explain the reduced tolerance of Asians to mercaptopurine. Whether polymorphisms of genes encoding enzymes involved in the folate metabolic pathway or perhaps other genes affect the response to antimetabolites in Asian populations requires further study.

Treatment of childhood ALL

Treatment with basic resources (Table 5)

In countries with basic resources, general practitioners with no formal training in administering chemotherapy may be the physicians who manage patients with cancer. Because drugs and supportive care are limited, our recommended treatment protocol for countries with basic resources incorporates drugs that are available in the WHO list of essential medications and are minimally myelosuppressive.

We propose a two-drug remission induction regimen with prednisolone and vincristine. Intrathecal methotrexate is recommended to prevent or treat central-nervous-system (CNS) leukemia, but the first dose may be delayed for up to a week to avoid excessive toxicity due to delayed methotrexate clearance in patients with renal impairment at diagnosis, and to reduce the risk of traumatic lumbar puncture with blast cells that can adversely affect treatment outcome.[40] Upon entering complete remission, patients will receive interim maintenance for 8 weeks with oral mercaptopurine or thioguanine (during a shortage of mercaptopurine) given daily at night (before bedtime) and weekly methotrexate alternating orally and intrathecally. Delayed intensification with dexamethasone, vincristine and intrathecal therapy is given twice and interrupted by a second interim maintenance phase, followed by maintenance therapy to complete a total treatment duration of 2 years. Although recent studies showed that a single 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 of our proposed protocol. In this regard, a former Children's Cancer Group study showed that a double-delayed intensification treatment in an overall non-intensive treatment protocol improved the outcome of patients with intermediate-risk ALL.[44] This proposed protocol is low-intensity, non-myelosuppressive and repetitive with little interruption. The repetitive blocks make it easy to train doctors and nurses on how to administer treatment. Approximately 50 to 70% of patients may go into remission and 20% may be cured with the two-drug induction, followed by maintenance therapy, based on treatment used in the U.S. in the 1960s.[45] Compared to three- or four-drug induction, the two-drug induction is less toxic and requires less supportive care that are generally limited in countries with basic resource, and will reduce abandonment rates. However, if asparaginase is affordable, it may be added for 2 to 3 weeks during remission induction because it is relatively non-myelosuppressive and may improve long-term survival rate to 30 to 50% according to the results of the Children's Cancer Group 100-series of studies. [46]

Treatment with limited resources (Table 6)

In countries with limited resources, efforts to train and certify oncologists and nurses are helpful in establishing a team of trained clinicians. A "twinning" program with an institution in a developed country can facilitate the development of an effective cancer treatment program in an institution with limited resources.[47,48] Internet-enabled communication tools

such as Cure4kids (www.cure4kids.org) by St Jude International Outreach Programme can be invaluable to training teams and managing difficult cases.

We recommend a three-drug induction protocol for all patients with added daunorubicin and extended L-asparaginase treatment for those with poor early response based on day 8 peripheral blood or day 15 bone marrow evaluation. The U.S. Children's Oncology Group's protocols featuring three-drug induction regimen (dexamethasone, asparaginase and vincristine without anthracyclines), a 4-week low-intensity consolidation phase, and no high-dose methotrexate have yielded excellent results, especially for standard-risk B-ALL cases.[28] A three-drug remission induction with only two doses of L-asparaginase had induced a 70.9% complete remission rate in a low-income province in Indonesia; induction failures consisted of abandonment in 12.1%, toxic deaths in 10.3%, and resistant disease in 6.7% of the patients.[49] Risk stratification is possible and desirable, and we propose that a higher dose of cyclophosphamide for consolidation treatment in high-risk cases because this drug improves outcome, especially for those with T-cell ALL.[50] In cases of high-risk ALL, intermediate-dose methotrexate (1 g/m^2 infusion over 24 hours with leucovorin rescue at 10 mg/m^2 starting at 42 hours and repeated every 6 hours for three doses) may also be added as part of the consolidation therapy with increased leucovorin rescue implemented on the basis of an elevated serum creatinine concentration. Dexamethasone is used for postremission therapy to improve systemic and CNS leukaemia control.[51] Triple intrathecal therapy is desirable for patients with T-cell ALL and those with leukemic blasts in cerebrospinal fluid.[40] Based on the results of MCP-841 protocol which features similar treatment and has been used in multiple centers in India,[52,53] up to 60 percent of the patients may be cured with this approach. We do not recommend routine prophylactic cranial irradiation because this modality is associated with many serious complications, and has not been convincingly shown to improve long-term survival in the context of effective systemic and intrathecal therapy, especially for patients with B-ALL.[4]

Treatment with enhanced or maximum resources (Table 6)

At centers with enhanced or maximal resources, it should be possible to adopt or modify one of the many risk-directed protocols developed in Asia, Western Europe or North America that have yielded excellent results.[12,14,35,41,54–57] In general, these protocols feature early intrathecal therapy, consolidation therapy with high-dose methotrexate for high-risk and T-cell ALL, a delayed intensification phase with dexamethasone, vincristine and asparaginase, and continuation therapy with mercaptopurine and methotrexate for 2 to 2.5 years. While hematopoietic stem cell transplantation with matched related donor may be recommended for 2 to 6% of very high-risk patients such as those with T-cell or Philadelphia chromosome-positive ALL and poor early response,[14,35,54] it generally improve long-term survival marginally as compared to patients treated with intensive chemotherapy only (e.g., from 36% to 45% in Philadelphia chromosome-positive ALL).[58] Tyrosine kinase inhibitor, if available, should be used in patients with Philadelphia chromosome-positive ALL because it can improve 3-year event-free survival from 35% to 80% without the use of transplantation.[59] If tyrosine kinase inhibitor is not available, patients with this genotype should be treated with the most intensive arm of chemotherapy and transplanted if response to remission induction treatment is poor.

Treatment of adult ALL

Basic resources

Since there are no published reports on the treatment of adult ALL in countries with basic resources, a similar approach to that for paediatric ALL patients can be recommended. However, the dosages of drugs should be tailored to the tolerance of adults. Referral to tertiary medical centres with adequate expertise and resources should be considered.

Philadelphia chromosome-negative ALL: limited, enhanced or maximum resources (Table 7)

Most chemotherapy regimens feature multiagent induction, intensification, consolidation and maintenance phases, together with CNS prophylaxis using intrathecal chemotherapy with or without cranial irradiation.[60,61] Hematopoietic 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.[5,62]

UKALL XII and hyperCVAD protocols have gained popularity recently because of their encouraging results.[61,63] The MRC UKALL XII/ECOG 2993 international trial featured a two-phase induction regimen with vincristine, prednisolone, daunorubicin, L-asparaginase, cyclophosphamide, cytarabine and mercaptopurine, followed by intensification with high-dose methotrexate and L-asparaginase.[61] Patients were then randomized for matched-sibling allogeneic transplantation, autologous transplantation or consolidation and maintenance chemotherapy. The overall complete remission rate for the 1153 Philadelphia chromosome-negative cases was 93% and the 5-year survival was 41%.[61] Poor-risk factors included age 35 years or older, high leukocyte count (>30 $x10^9$/L for B-ALL and >100 $\times 10^9$/L for T-cell ALL), and B-lineage. This regimen yielded a comparable outcome, with a complete remission rate of 85% and an estimated 5-year survival of 40%, when used in a Singapore center.[64]

The hyperCVAD protocol was 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.[63] G-CSF support was used during the intensive chemotherapy cycles. CNS-directed therapy consisted of intrathecal therapy with methotrexate and cytarabine only, and cranial irradiation was not included. In the single center study of 288 patients, the overall complete remission rate was 92% and the 5-year survival was 38%, which were remarkably similar to results of the UKALL XII/ECOG 2993 trial.[63] Advanced age, poor performance status, high leukocyte count and Philadelphia chromosome-positivity were associated with a poor outcome. In a retrospective analysis of 53 adult ALL patients in a single center in China, treatment with hyperCVAD resulted in a complete remission rate of 73.6% and a 2-year survival of 82.9%.[65] We therefore recommend these two regimens as initial therapy for adult ALL patients.

Role of allogeneic transplantation in Philadelphia chromosome-negative ALL: enhanced or maximum resources (Table 7)

In view of the suboptimal outcome of adult ALL patients treated with chemotherapy alone and the dismal survival following relapse, the role of allogeneic transplantation has been evaluated for patients in first remission.[62,66] Several large clinical trials have compared the efficacy of allogeneic transplantation versus other approaches for adult ALL patients in first remission and yielded similar conclusions.[67–69] The MRC UKALL XII/ECOG 2993 was the largest prospective trial to examine the impact of allogeneic transplantation, chemotherapy alone and autologous transplantation on survival.[67] When a donor versus no-donor analysis was used, Philadelphia chromosome-negative ALL patients with donors were found to have a significantly better 5-year survival (53% vs. 45%) and a lower relapse rate.[67] In this study, high-risk disease was defined by age older than 35 years, high leukocyte count or prolonged induction (more than 4 weeks) to achieve complete remission. The lower relapse rate associated with allogeneic transplantation was demonstrated in both high-risk and standard-risk patients, whereas the benefit in survival was only significant in standard-risk group partly because of the increased transplant-related mortality in the high-risk group, especially in older patients. There was no difference in survival between patients who received chemotherapy alone and those undergoing autologous transplantation.[67] The Cochrane review that analyzed 14 relevant clinical trials also supported the use of matched-sibling donor allogeneic transplantation as the optimal post remission treatment in ALL patients aged 15 years or over.[70] A recent meta-analysis also concluded that matched-sibling donor allogeneic transplantation improved survival; however, it improved outcome only in younger patients < 35 years of age and the absolute benefit in survival was only approximately 10 percent.[71] Based on the current evidence, matched-sibling donor allogeneic transplantation should be considered for adults with Philadelphia chromosome-negative ALL, especially those with a younger age.

Treatment of Philadelphia chromosome-positive ALL (Table 7)

Before the era of tyrosine kinase inhibitors (TKIs), allogeneic transplantation (related or unrelated) in first remission, whenever possible, was recommended in adults with Philadelphia chromosome + ALL because it improved 3-year survival to 36–40%.[72] Recent addition of imatinib mesylate or dasatinib (a second-generation TKI that can overcome several imatinib-resistant *ABL* kinase domain mutations) to frontline chemotherapy significantly increased the remission rates to over 90% without adding systemic toxicities, and when given before and after allogeneic transplantation, improved disease-free survival to 60–75%.[73,74] For patients without a donor, continuation of chemotherapy with a TKI is recommended. For those older than 60 years old who are ineligible for transplantation, use of TKI as a single agent or combined with standard regimens was well tolerated and improved outcome.[75,76] While longer follow-up is needed to ascertain the durability of such approaches, we recommend treatment of older Philadelphia chromosome + ALL patients who are precluded from intensive therapies with a TKI combined with corticosteroids or with chemotherapy regimens as tolerated. The emergence of resistance to TKIs remains a challenge. Current trials are testing the third generation TKI ponatinib, which shows

promising activity against a variety of *ABL* kinase domain mutations including the T315I mutation.[77]

Supportive care

Timely and effective supportive care is critical for the successful treatment of ALL. Indeed, the intensity of treatment for ALL must be appropriate for the level of supportive care that is available. Indiscriminate adoption of high-intensity treatments from developed countries is inappropriate, without a commensurate level of supportive care. Over-treatment beyond the limits of supportive-care capabilities can lead to excessive induction death and high abandonment rates.[78] Currently in countries with basic, and even limited resources, the induction death rate is approximately 30%, exceeding even the total cumulative risk of relapse.[79–81] Deaths from infection and bleeding are most common. In one study from Northern India, sepsis and bleeding accounted for 53.3% and 15.7% of deaths, with tumour lysis syndrome contributing to 6.3% of deaths.[81] Adequate hydration and allopurinol before commencement of steroid or other chemotherapy must be instituted. Table 8 lists a number of supportive treatment regimens according to the level of available resources. Hunger et al[82] have also outlined step-up treatment protocols that may still be too intensive for countries with basic and limited resources in Asia. Recently the PODC (Paediatric Oncology in Developing Countries) 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. Patients on chemotherapy should preferably 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 the 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 preventing *Pneumocystis jiroveci* pneumonitis. A febrile-neutropenia protocol based on local bacterial sensitivity should be developed so that nurses and junior physicians can initiate treatment without delay.

Malnutrition is common among Asian children (Table 2). According to Unicef, 17% of children under 5 years of age in East Asia/Pacific and 46% in Southeast Asia are underweight.[85] Malnutrition can develop within days after anticancer treatment in children,[86] and may be associated with impaired immunity, decreased tolerance to chemotherapy, increased infection rates, and consequently decline in the overall outcome.[87–90] It is also noted that children with ALL receiving chemotherapy tend to suffer from intestinal parasitic diseases.[91]

Managing patients with tuberculosis

Tuberculosis is endemic in Asia. The incidence of tuberculosis in children with ALL is 10–22 times that of children from similar backgrounds and ~50% of patients with active tuberculosis at presentation show reactivation within 5 months after completion of remission

induction therapy.[92] The two most common forms of infection are pulmonary and meningeal tuberculosis. Culture and sensitivity testing for multi-resistant *M. tuberculosis* is important. Initial therapy with isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months followed by isoniazid and rifampicin for 4 months is needed. Miliary tuberculosis requires prolonged treatment for 12 months to reduce the risk of reactivation. Chemotherapy should not be delayed for prolonged times, and antituberculosis drugs can be started simultaneously with chemotherapy. Patients may need more than one course of anti-tuberculosis treatment as reactivation is common. Family members must be screened and treated for tuberculosis. Combination anti-tuberculosis medications in a single pill are available in many Asian countries and may improve treatment compliance. In endemic areas, routine Mantoux test and chest X-ray are recommended for all newly diagnosed ALL patients. A positive Mantoux test (induration > 20 mm) will require investigations to isolate *Mycobacterium tuberculosis*. In most countries, early morning gastric aspirate or induced sputum using nebulized normal saline for 3 consecutive days to look for acid-fast bacilli and tuberculosis culture and sensitivity is recommended. In countries with maximal resources, broncho-alveolar lavage is also acceptable. Since latent tuberculous may reactivate during the early months of chemotherapy, prophylactic treatment with rifamcipin for at least 6 months is commonly practiced, even without a definite focus of infection or positive culture.

Managing patients with hepatitis B

Asia is home to 75% of the 400 million of hepatitis B virus (HBV) carriers in the world. The prevalence of chronic HBV carriers is high in Asia with the highest rates (~8% to 20%) in Southeast Asia, China, Central Asia and the Middle East. Most are acquired from vertical transmission from maternal hepatitis B carriers or early during childhood. Active neonatal hepatitis B vaccination programmes in most Asian countries promises 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 of hepatitis B virus at diagnosis of ALL may reduce transfusion-acquired HBV infection. Intensive chemotherapy or transplantation may reactivate chronic hepatitis B infections in carriers and may adversely affect treatment. We recommend routine testing of liver function, HBsAg, anti-HBs Ab and anti HBcore Ab at diagnosis in countries with enhanced or maximal resources. The presence of HBsAg indicates a chronic carrier state, and the need for regular quantitative monitoring for HBV DNA titres during treatment. Carriers with high HBV DNA titres or elevated liver enzymes may require anti-viral therapy with oral nucleos(t)ides such as lamivudine, entecavir or tenofovir. In patients who have high HBV titers or prolonged treatment with lamivudine, entacavir may be preferable because of emerging concern about the development of resistance to lamivudine.[94,95] Detection of anti-HBc Ab suggests a history of previous natural infection. Monitoring HBV DNA titres is recommended when there are prolonged unexplained elevated liver enzymes or conjugated hyperbilirubin in patients who are anti-HBc Ab positive. In countries with basic and limited resources where antiviral therapy is not available, routine monitoring for HBV immune status is not done. Routine testing for HBsAg and anti-HCV in all blood products is critical to protect all patients.

Transfusion support

In countries with basic or limited resources, safe blood components such as platelets and red cells may not be readily available; blood banks may not even be opened daily. For these countries, directed family donors are commonly used 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 with transfusion-dependent anaemia in Southeast Asia, may help provide additional units of random platelets. Local government plays 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 cells and random platelets. Government and other public organizations should work together more closely to raise public awareness over the importance of voluntary blood donation.

Pain control

The WHO guideline on pain control recommends a two-step approach which is effective in about 90% of patients.[96] Mild pain can be managed with oral paracetamol; nonsteroidal anti-inflammatory drugs should be avoided because thrombocytopenia is common in patients with leukemia. Non-pharmacologic approaches such as distraction, controlled breathing and provision of appropriate anticipatory guidance should always be used concomitantly with pharmacologic approaches. For moderate-to-severe pain, opiates are necessary. Morphine is the first-line opioid. However, 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 requires conversion by cytochrome P450 2D6 to active morphine in vivo; some poor metabolizers lack response to codeine while other ultra-rapid metabolizers are at risk of toxicity with “normal” doses of codeine.[39] The Asian Oncology Summitt guideline on palliative care noted that only in about seven Asian countries patients with cancer have access to more than 1 mg of morphine per head, a measure considered adequate access to pain relief drugs.[97] This limitation may be lessened because WHO has made access to morphine 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 lack of treatment facility and monitoring devices. The procedure-related pain can induce substantial short-term and long-term anxiety and psychological sequelae. Local analgesia using EMLA cream and subcutaneous lignocaine and conscious sedation such as intravenous midazolam should be given before the painful procedures. Training of staffs in safe administration of sedation should be in place, from monitoring to resuscitation.[98]

Antiemetics

Setrons, 5-hydroxytryptamine antagonists, are highly effective in preventing nausea and vomiting in frontline ALL treatments for both children and adults, but represent the second most expensive supportive care after parenteral antibiotics. In general, chemotherapy used to treat ALL is not strongly ematogenic. Non-setron antiemetics may be used as alternatives. Intravenous metoclopramide, combined with intravenous diphenhydramine to reduce the

risk of oculo-gyric crisis, can be used effectively in countries with basic resources when patients or their families cannot afford setrons. Lorazepam and chlorpromazine may be helpful in some patients.[99,100] Asian governments should consider subsidising generic ondansetron as it is cost-effective and makes ALL therapy more tolerable. Patients with ultra-rapid metabolizing CYP2D6 variants may not respond to ondansetron and require granisetron.[101]

Psychosocial support and palliative care

Abandonment or poor adherence to chemotherapy due to the high cost of treatment and travel to treatment centers, as well as loss of income, are major contributors to treatment failure in low-income countries.[102,103] Besides social support to enable patients to complete treatment, an education program for parents could markedly improve outcome.[104]

Palliative service also plays an integral role in the provision of high-quality care but is still a relatively new subspecialty under development in many low-income countries.[105] In many Asian countries, palliative care is not fully funded by governments, and is inadequate because the staffs are not well trained and the communities are not well informed, especially in paediatrics. Integration of palliative care through 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 optimal model for high-quality comprehensive care for adults and children with cancer.[108] Table 9 summarizes some of the key components of palliative care. Paediatric palliative care programs should be started, leaning on the experience and resources of better-established adult palliative care programs.

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Search strategy and selection criteria

We searched Medline and PubMed for articles published in English from 2000, with the search 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 seer.cancer.gov, unescap.org, who.int and unicef.org.

Table 1

Patient characteristics and treatment results from selected clinical trials enrolling children with ALL in Asia

Study	Year of Study	No. of Patients	Age range (yr.)	Median WBC x 10^9/L	T-cell %	*BCR-ABL1* %	Outcome, %		Data Source
							Event-free survival	Survival	
CHINA									
BCH-2003/CCLG-2008	2003–2010	1004	0–16	NA	10.2	6.5	82.6 ± 1.5 at 5 yr for BCH-2003; 82.9 ± 2.4 at 3 yr for CCLG-2008	NA	Gao C, et al[6]
TPOG-2002	2002–2007	788	1–18	NA	9.7	4.4	77.4 ± 1.7 at 5 yr	83.5 ± 1.6 at 5 yr	Liang D-C, et al[7]
HK 93/97	1997–2002	171	1–17	12.6	14	3.5	79 at 4 yr	86.5 at 4 yr	Li CK, et al[8]
INDIA									
Modified BFM 76/79	1985–2003	307	1–14	10	22	5.7	*56 ± 3.2 at 5 yr	*59.8 ± 2.3 at 5 yr	Bajel A, et al[9]
MCP-841	1992–2002	254	1–15	NA	31	---	51.6 ± 3.8	69.1 ± 4.1	Arya LS, et al[10]
JAPAN									
TCCSG L95-14	1995–1999	597	1–15	~10	9.7	4.0	76.8 ± 1.8 at 5 yr	84.9 ± 1.5 at 5 yr	Tsuchida M, et al[11]
JCCLSG ALL 2000	2000–2004	305	1–15	NA	9.8	0	†79.7 ± 2.4 at 5 yr	†89.2 ± 1.8 at 5 yr	Yamaji K, et al[12]
KYCCSG ALL-96	1996–2002	201	1–15	7.3	10.4	4.9	§72.1 at 7 yr	§84.8 at 7 yr	Nagatoshi Y, et al[13]
SINGAPORE									
Ma-Spore ALL 2003	2002–2011	556	0–18	NA	8.8	4.0	80.6 ± 3.5 at 6 yr	88.4 ± 3.1 at 6 yr	Yeoh AEJ, et al[14]
KOREA									
B-ALL	2004–2008	98	NA	NA	0	NA	NA	88.8 ± 5.3 at 3 yr	Koh KN, et al[15]

*Censored 30 patients stopped treatment or lost to follow-up;

†excluded patients with t(9;22);

§excluded patients with t(9;22) or t(4;11)

Table 2

Health-related statistics in selected Asian countries

Country	Total Population (x1,000)	Population Aged 0–14 (%)	Number of Physician (/ 10,000 population)	Number of Nurses and Midwives (/ 10,000 population)	Tuberculosis Prevalence Rate (/ 100,000 population)	Underweight Among Children Under 5 years (%)	Under 5 Mortality Rate (/ 1,000 births)	Measles Immunization Coverage Among Children Under 1 year (%)	Annual Government Expenditure Per Capita (USD)	Annual Total Health-care Expenditure Per Capita (USD)
Basic resource										
Myanmar	48,337	25.2	5	8	525	29.6	62	88	4	34
Afghanistan	32,358	46	2	5	352	32.9	101	62	5	44
Bangladesh	150,494	30.6	3	3	411	41.3	46	94	19	57
Pakistan	176,745	34.8	8	6	364	31.3	72	86	23	59
Nepal	30,486	35.4	2	5	238	38.8	48	86	22	66
Timor-Leste	1,154	45.7	1	22	643	45.3	54	66	47	84
Lao PDR	6,288	33.6	3	10	130	36.4	42	64	32	97
Limited resource										
Indonesia	242,326	26.7	3	20	289	19.6	32	89	55	112
Cambodia	14,305	31.2	2	8	660	28.8	43	93	45	121
India	1,241,492	30.2	6	13	256	43.5	61	74	39	132
Philippines	94,852	35	12	60	502	20.7	25	88	50	142
Sri Lanka	21,045	24.9	5	19	101	21.6	12	99	66	148
Vietnam	88,792	23.2	12	10	334	20.2	22	98	81	215
Mongolia	2,800	27.5	28	35	331	5.3	31	97	120	218
Bhutan	738	28.8	<1	3	181	12.7	54	95	239	275
Enhanced resource										
Thailand	69,519	20.2	3	15	182	7	12	98	247	330
China	1,347,565	19.1	14	14	108	3.4	15	99	203	379
Maldives	320	25.8	16	45	13	17.8	11	97	281	464
Malaysia	28,859	29.9	9	27	107	12.9	7	96	356	641
Brunei	406	25.9	14	49	91	n/a	7	94	1,230	1,449

Country	Total Population (x1,000)	Population Aged 0–14 (%)	Number of Physician (/ 10,000 population)	Number of Nurses and Midwives (/ 10,000 population)	Tuberculosis Prevalence Rate (/ 100,000 population)	Underweight Among Children Under 5 years (%)	Under 5 Mortality Rate (/ 1,000 births)	Measles Immunization Coverage Among Children Under 1 year (%)	Annual Government Expenditure Per Capita (USD)	Annual Total Health-care Expenditure Per Capita (USD)
Maximum resource										
Republic of Korea	48,391	16	20	53	151	n/a	5	98	1,193	2,023
Singapore	5,188	16.9	18	59	44	3.3	3	95	825	2,273
New Zealand	4,415	20.4	27	109	9	n/a	6	91	2,514	3,020
Japan	126,497	13.3	21	41	27	n/a	3	94	2,644	3,204
Australia	22,606	18.9	30	96	8	n/a	5	94	2,340	3,441

Table 3

Recommendations for diagnostic workup depending on resource availability

	Paediatrics	**Adults**
Basic	Morphology ± cytochemistry, CXR – mediastinal mass	Morphology ± cytochemistry, CXR – mediastinal mass
Limited	Morphology and cytochemistry, Immunophenotyping (limited), DNA index, RT-PCR for *BCR-ABL1*, *MLL-AFF1*, *ETV6-RUNX1*	Morphology and cytochemistry, Immunophenotyping (limited to exclude acute myeloid leukemia and mixed-lineage acute leukemia), RT-PCR for *BCR-ABL1*, Cytogenetics for Philadelphia chromosome or FISH for *BCR-ABL1*
Enhanced	Morphology, Immunophenotyping, DNA index, RT-PCR for *BCR-ABL1*, *MLL-AFF1*, *ETV6-RUNX1*, *TCF3-PBX1*, Cytogenetics for hyperdiploid>50 or hypodiploid<44, FISH – chromosomes 4, 10, 17, *BCR-ABL1*	Morphology, Immunophenotyping, RT-PCR for *BCR-ABL1*, *MLL-AFF1*, Cytogenetics for hyperdiploid>50, FISH –*BCR-ABL1*, HLA typing
Maximal	Same as enhanced, Genome-wide analysis, Pharmacogenetics	Same as enhanced, Genome-wide analysis, Pharmacogenetics

Table 4

Recommendation for risk assignment based on resource availability

	Paediatrics	**Adults**
Basic	Age, leukocyte count, day 8 peripheral blood response	Age, leukocyte count, day 8 peripheral blood response
Limited	Age, leukocyte count, immunophenotype (T-cell vs. B-cell), prednisone response or day 8 peripheral blood or bone marrow response, day 15 and end of induction bone marrow response; If available, *BCR-ABL1*, *MLL-AFF1*, *ETV6-RUNX1*	Age, leukocyte count, immunophenotype (T-cell vs. B-cell), prednisone or day 8 peripheral blood or bone marrow response, end of induction bone marrow response. If available, RT-PCR for *BCR-ABL1*, cytogenetics for Philadelphia chromosome or FISH for *BCR-ABL1*
Enhanced	Same as limited, ± DNA index, RT-PCR for *BCR-ABL1*, *MLL-AFF1*, *ETV6-RUNX1*, *TCF3-PBX1*, Cytogenetics for hyperdiploid>50 and hypodiploid<44, FISH – chromosome 4, 10, 17, *BCR-ABL1*	Same as limited, RT-PCR for *BCR-ABL1*, *MLL-AFF1*, Cytogenetics for hyperdiploid>50, FISH –*BCR-ABL1*, HLA typing
Maximal	Same as enhanced, Minimal residual disease measurements by IgH/TCR rearrangements, flow cytometry or deep sequencing, Genome-wide analysis to identify lesions responsive to ABL tyrosine kinase inhibitors, Pharmacogenetics	Same as enhanced, Minimal residual disease measurements by IgH/TCR rearrangements, flow cytometry or deep sequencing, ABL-kinase domain mutation analysis, especially the T315I mutation for selection of alternative tyrosine kinase inhibitors, Pharmacogenetics

Table 5

Proposed ALL protocol for children and adults in countries with basic resources.

Basic (Non-risk stratified)
Induction (2-drug) – 1 month Vincristine* 1.5 mg/m^2 per dose on days 1,8,15, and 22 Prednisolone 40 mg to 60 mg/m^2 per day x 28 days L-Asparaginase (if available) 6000 U/m^2 per dose on days 4, 6, 8, 11, 13, 15 Intrathecal methotrexate on days 8, 15 and 22
Interim maintenance #1 (8 weeks) Mercaptopurine 37.5 to 50 mg/m^2 or thioguanine** 30 to 40 mg/m^2 per night Oral methotrexate 15 to 20 mg/m^2 per dose on weeks 2, 4, 6, and 8 Intrathecal methotrexate on weeks 1,3, 5 and 7
Delayed intensification #1 (4 weeks) Vincristine* 1.5 mg/m^2 per dose on days 1,8,15, and 22 Dexamethasone 4 to 6 mg/m^2 per day x 28 days Intrathecal methotrexate on days 1 and 15
Interim maintenance #2 (8 weeks) Same as interim maintenance #1
Delayed intensification #2 (4 weeks) Same as delayed intensification #1
Maintenance (4-week block repeated until 2 years) Mercaptopurine 37.5 to 50 mg/m^2 or thioguanine* 30 to 40 mg/m^2 per night x 28 days Oral methotrexate 15 to 20 mg/m^2 per week x 4 weeks Dexamethasone 4 to 6 mg/m^2 per day for 5 days on week 3 Vincristine* 1.5 mg/m^2 per dose on week 3

* The maximum dose of vincristine should be capped at 2 mg.

** Prolonged thioguanine treatment can be associated with veno-occlusive disease of liver and thrombocytopenia, and should only be used when mercaptopurine is not available.

Table 6

Proposed ALL protocol for children in countries with limited, enhanced or maximal resources.

Limited	Enhanced/Maximal
Induction (3-drug, Risk stratified) – 1 month Prednisolone 40 to 60 mg/m^2 per day x 28 days for standard-risk ALL Dexamethasone 6 mg/m^2 per day x 28 days for high-risk ALL Vincristine* 1.5 mg/m^2 per dose on days 1,8,15 and 22 L-asparaginase 6,000 U/m^2 per dose on days 4,6, 8,11, 13, 15 Daunorubicin 30 mg/m^2 on day 15 and L-asparaginase 6,000 U/m^2 on days 18, 20 and 22 may be added for poor early responders Intrathecal methotrexate on days 8, 15 and 22	Induction (3 to 4 drug, Risk stratified) – 1 month Prednisone 40 to 60 mg/m^2 per day or Dexamethasone 6 mg/m^2 per day x 28 days Vincristine* 1.5 mg/m^2 per dose on days 1,8,15 and 22 L-asparaginase 6,000 to 10,000 U/m^2 per dose on days 4,6, 8,11, 13, 15 or pegylated L-asparaginase 1000 U/m^2 on day 3 or 4 Daunorubicin 25 mg/m^2 on days 1and 8 added for high-risk ALL L-asparaginase 10,000 U/m^2 on day 18, 20 and 22 or pegylated L-asparaginase 1000 U/m^2 on day 15 may be added for high-risk ALL or poor early responders Intrathecal methotrexate on days 1 and 15 and added on days 8 and 22 for patients at increased risk of CNS relapse
Consolidation – 3 to 4 weeks Intravenous cyclophosphamide 250 mg/m^2 on day 1 for standard-risk Intravenous cyclophosphamide 500 mg/m^2 on day 1 for high-risk ALL Subcutaneous cytarabine 75 mg/m^2 per day x 4 days Mercaptopurine 37.5 to 50 mg/m^2 or thioguanine** 30 to 40 mg/m^2 per night x 14 days Intrathecal methotrexate on days 1 and 15	Consolidation I – 3 to 4 weeks Intrathecal cyclophosphamide 1000 mg/m^2 on day 1 Intrathecal cytarabine 75 mg/m^2 on days 1 to 4 and days 8 to 11 Mercaptopurine 50 to 60 mg/m^2 per night on days 1 to 14 Intrathecal Methotrexate on day 1 Consolidation II – 8 weeks High-dose methotrexate 1 to 2.5 g/m^2 for low-risk and 5 g/m^2 for high-risk ALL on days 1, 15, 29 and 43 Mercaptopurine 25 mg/m^2 per night from days 1 to 56 Intrathecal methotrexate on day 1, 15, 29 and 43
Interim therapy #1 (after recovery from consolidation therapy) – 8 weeks Mercaptopurine 37.5 to 50 mg/m^2 or thioguanine** 30 to 40 mg/m^2 per night Oral methotrexate 15 to 20 mg/m^2 on weeks 2 and 4 to 8 Intrathecal methotrexate on weeks 1 and 3	Delayed intensification and maintenance therapy (2 to 2.5 years) according to one of the following protocols: **1** JCCLSG ALL 2000[12] or **2** Ma-Spore 2003[14] or **3** St. Jude Total Therapy Study 15[35] or **4** UKALL 2003[41] or **5** BFM protocol[54] or **6** COG protocol[55] or **7** DCOG ALL-9 [56] or **8** DFCI 00-01[57]
Delayed intensification #1 – 4 weeks Vincristine* 1.5 mg/m^2 per dose on days 1,8,15 and 22 Dexamethasone 6 mg/m^2 per day x 28 day L-asparaginase 10,000 U/m^2 per dose on days 3,6,9, 12, 15 and 18 for standard-risk L-asparaginase 10,000 U/m^2 per dose on days 3,6,9,12,15,18, 21 and 24 for high-risk	

Limited	Enhanced/Maximal
Intrathecal methotrexate on days 1 and 15 Additional therapy for high-risk ALL only – 4 weeks Intravenous cyclophosphamide 500 mg/m^2 on day 1 Subcutaneous cytarabine 75 mg/m^2 per day x 4 days Mercaptopurine 37.5 to 50 mg/m^2 or thioguanine** 30 to 40 mg/m^2 per night x 28 days Intrathecal methotrexate on days 1 and 15	
Interim therapy #2 – 8 weeks Mercaptopurine 37.5 to 50 mg/m^2 or thioguanine** 30 to 40 mg/m^2 per night Oral methotrexate 15 to 20 mg/m^2 on weeks 2 to 8 Intrathecal methotrexate on week 1	
Delayed intensification #2 – 4 weeks – for high-risk ALL only Vincristine* 1.5 mg/m^2 per dose on days 1,8,15, and 22 Dexamethasone 6mg/m^2 per day x 28 day L-asparaginase 10,000 U/m^2 per dose on days 3,6,9,12,15,18,21 and 24	
Intrathecal methotrexate on days 1 and 15 Additional therapy for high-risk ALL only – 4 weeks Intravenous cyclophosphamide 500 mg/m^2 on day 1 Subcutaneous cytarabine 75 mg/m^2 per day x 4 days Mercapotpurine 37.5 to 50 mg/m^2 or thioguanine** 30 to 40 mg/m^2 per night Intrathecal methotrexate on days 1 and 15	
Maintenance (4-week block repeated until 2 years) Mercaptopurine 37.5 to 50 mg/m^2 or thioguanine** 30 to 40 mg/m^2 per night x 28 days Oral methotrexate 15 to 20 mg/m^2 per week x 4 weeks Dexamethaosone 4 mg/m^2 per day x 5 days on week 3 Vincristine* 1.5 mg/m^2 per dose on week 3	

* The maximum dose of vincristine should be capped at 2 mg.

** Prolonged thioguanine treatment can be associated with veno-occlusive disease of liver and thrombocytopenia, and should only be used when mercaptopurine is not available.

Table 7

Proposed ALL protocols for adults in countries with limited, enhanced and maximal resources

	Philadelphia chromosome-negative ALL	**Philadelphia chromosome-positive ALL**
Chemotherapy regimens	**1** UKALL XII protocol, or **2** Hyper-CVAD regimen	**1** UKALL XII protocol, or **2** Hyper-CVAD regimen *PLUS* tyrosine kinase inhibitor (imatinib mesylate or dasatinib) for countries with enhanced and maximal resources
Allogeneic haematopoietic stem cell transplantation (for countries with enhanced and maximal resources)	Should be considered for all eligible patients with matched-sibling donors in first complete remission	Should be considered for all eligible patients with matched related or unrelated donors in first complete remission

Table 8

Recommendation for supportive care for children and adults with ALL

	Paediatrics	**Adults**
Basic	*Anti-emetics*: metoclopramide + diphenhydramine, lorazepam, chlorpromazine, dexamethasone *Analgesics*: parecetamol, codeine, morphine *Antibiotics:* cephalosporins, antipseudomonas semisynthetic penicillins, aminoglycosides, trimethoprim-sulfamethoxazole. *Blood products*: whole blood (directed), platelets *Prevention of tumour lysis*: allopurinol	*Anti-emetics*: same as Paediatrcis basic + ondansetron *Analgesics*: same as Paediatrics basic *Antibiotics*: same as Paediatrics basic. *Blood products*: same as Paediatrics basic *Prevention of tumour lysis*: same as Paediatrics basic
Limited	*Anti-emetics*: Basic + ondansetron *Analgesics*: intravenous midazolam + ketamine for painful procedures, codeine, methadone, morphine (multiple formulations) *Antibiotics:* broad-spectrum antibiotics, amphotericin B. *Prophylaxis*: trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* *Blood products*: packed red blood cells, platelets. *Prevention of tumour lysis*: allopurinol	*Anti-emetics*: same as Paediatris limited + ondansetron/granisetron *Analgesics*: parecetamol, codeine, methadone, morphine (multiple formulations) *Antibiotics*: same as Paediatrics limited + azoles *Prophylaxis*: trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* *Blood products*: packed red blood cells, single donor platelets *Prevention of tumour lysis*: allopurinol
Enhanced and Maximal	*Anti-emetics*: ondansetron, granisetron, aprepitant. *Analgesics*: central venous catheters, sedation/general anesthesia for painful procedures, fentanyl and other opioids *Antibiotics*: broad spectrum antibiotics, carbepenam, azoles, echinocandins *Prophylaxis*: trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* Hepatits B carriers – lamivudine, entecavir, tenofovir *Blood products*: leucocyte-depleted or irradiated blood components, single-donor platelets *Prevention of tumour lysis*: allopurinol ± rasburicase	*Anti-emetics*: same as Paediatrics enhanced *Analgesics*: central venous catheters, sedation/general anesthesia for painful procedures, intravenous morphine, fentanyl *Antibiotics*: broad spectrum antibiotics, carbepenam, azoles, echinocandins, liposomal amphotericin B. *Prophylaxis*: trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* Acyclovir prophylaxis for herpes simplex, varicella zoster HepB carriers – lamivudine, entecavir, tenofovir *Blood products*: leukocyte-depleted or irradiated blood components, single-donor platelets, HLA-matched platelets *Nutrition:* total parenteral nutrition *Prevention of tumour lysis*: allopurinol ± rasburicase

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Table 9

Recommendation for palliative care for children and adults with ALL

	Paediatrics	**Adults**
Basic	*Pain control*: parecetamol, codeine, immediate-release oral morphine, dexamethasone *Nausea/vomiting*: metoclopramide + diphenhydramine, lorazepam, chlorpromazine, promethazine, dexamethasone *Dyspnoea*: codeine, morphine, chlorpromazine, lorazepam	*Pain control*: Same as Paediatrics basic *Nausea/vomiting*: metaclopramide, prochloperazine, lorazepam, ondansetron, dexamethasone *Dyspnoea*: Same as Paediatrics Basic
Limited	*Pain Control*: immediate release oral morphine, neuropathic pain adjuvant (e.g., gabapentin) *Nausea/vomiting*: Basic + ondansetron *Dyspnea*: oxygen, diazepam, morphine *Psycho-social support: parent support groups*	*Pain Control*: Basic + slow release oral morphine, neuropathic pain adjuvant (e.g., amytriptyline) *Nausea/vomiting*: Basic + granisetron *Dyspnea*: oxygen, morphine *Psycho-social support* including hospice
Enhanced and Maximal	*Pain control*: transdermal morphine (e.g., fentanyl patch), intravenous/patient-controlled analgesia morphine, palliative chemotherapy, slow release oral morphine, neuropathic pain adjuvants (e.g., gabapentin, carbamazepine) *Nausea/vomiting*: ondansetron/granisetron, dexamethasone *Dyspnoea*: intravenous/patient-controlled analgesia morphine, diazepam/lorazepam *Bleeding and anemia*: blood products *Psycho-social support* including hospice, bereavement support	*Pain control*: Same as Paediatrics enhanced + methadone, neuropathic pain adjuvants (e.g., amitriptyline, gabapentin, carbamazepine) *Nausea/vomiting*: Same as Paediatrics enhanced *Dyspnoea*: Same as Paediatrics enhanced *Bleeding and anemia*: blood products *Psycho-social support* including hospice, bereavement support