Childhood acute lymphoblastic leukaemia – current status and future perspectives

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The current cure rate of 80% in childhood acute lymphoblastic leukaemia attests to the effectiveness of risk-directed therapy developed through well-designed clinical trials. In the past decade there have been remarkable advances in the definition of the molecular abnormalities involved in leukaemogenesis and drug resistance. These advances have led to the development of promising new therapeutic strategies, including agents targeted to the molecular lesions that cause leukaemia. The importance of host pharmacogenetics has also been recognised. Thus, genetic polymorphisms of certain enzymes have been linked with host susceptibility to the development of *de novo* leukaemia or therapy-related second cancers. Furthermore, recognition of inherited differences in the metabolism of antileukaemic agents has provided rational selection criteria for optimal drug dosages and scheduling. Treatment response assessed by measurements of submicroscopic leukaemia (minimal residual disease) has emerged as a powerful and independent prognostic indicator for gauging the intensity of therapy. Ultimately, treatment based on biological features of leukaemic cells, host genetics, and the amount of residual disease should improve cure rates further.

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The 5-year event-free survival of children with acute lymphoblastic leukaemia (ALL) treated with contemporary risk-directed therapy ranges from 63–83% in developed countries (Figure 1, Table 1).[1–9] With retrieval therapy for those who suffer a relapse, 80% or more of patients can be cured. Current efforts to improve cure rate further include:

- precise risk assessment to avoid over-treatment or under-treatment;
- pharmacodynamic and pharmacogenomic studies to optimise therapy;
- molecular genetic studies of leukaemic cells and pharmacogenomic studies of host normal cells to elucidate the mechanisms of leukaemogenesis and drug resistance; and,
- the development of more specific therapies.

In this article, we review the current status of the biological studies of childhood ALL and treatments that are in use, and we suggest future directions.

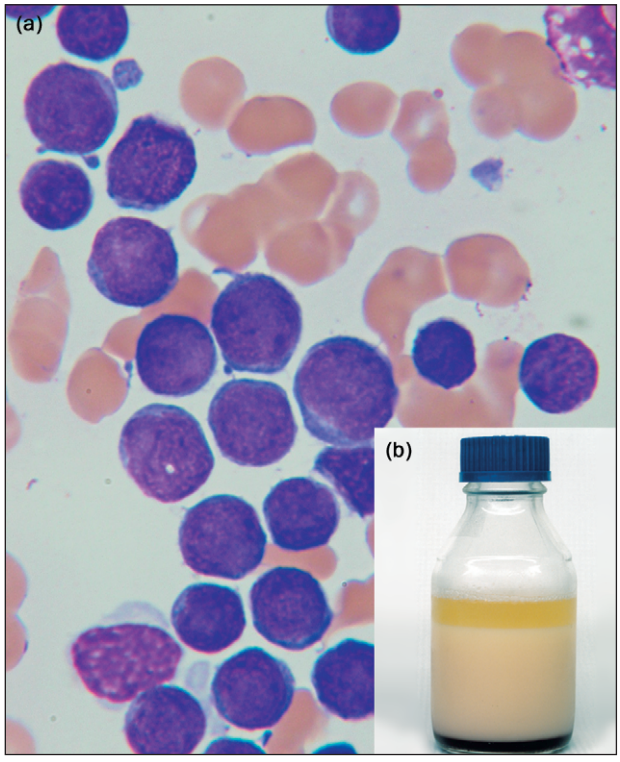

Figure 1. (a) Acute lymphoblastic leukaemia cells are generally fairly small, with scanty cytoplasm, homogeneous nuclear chromatin and inconspicuous nucleoli (Wright-Giemsa, x 1000). (b) The flask shown contains a leukapheresed sample from a patient with acute lymphoblastic leukaemia, presenting with hyperleucocytosis and illustrates the definition of the term leukaemia (white blood). The upper layer represents plasma and the lower layer red cells.
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Table 1. Current results of international studies of childhood acute lymphoblastic leukaemia*

Study	Year	Years of eligible age	Number of patients	% 5-year event-free survival (SE)			
				Overall	B-lineage† Standard	B-lineage† High	T-lineage
AIEOP-91	1991–95	≤ 15	1194	70.8 (1.3)	79.9 (1.5)	61.5 (2.9)	40.4 (4.1)
BFM-90	1990–95	≤ 18	2178	78.0 (0.9)	87.4 (1.0)	66.3 (2.1)	61.1 (2.9)
CCG-1800	1989–95	≤ 21	5121	75 (1)	80 (1)	67 (2)	73 (2)
COALL-CLCG-92	1992–97	≤ 18	538	76.9 (1.9)	82.1(2.4)	75.7 (3.9)	71.2 (5.1)
DCLSG-7	1988–91	≤ 15	218	65.3 (3.2)	69.3 (4.1)	66.6 (7.6)	57.7 (8.6)
DFCI-91–01	1991–95	≤ 18	377	83 (2)	85 (2)	82 (4)	79 (8)
EORTC-58881	1989–98	≤ 18	2065	70.9 (1.1)	78.4 (1.3)	57.3 (2.4)	64.4 (2.9)
NOPHO-III	1992–98	≤ 15	1143	77.6 (1.4)	85.2 (1.5)	67.9 (3.3)	61.3 (4.9)
POG	1986–94	≤ 21	3828	70.9 (0.8)	77.4 (0.9)	55.3 (1.6)	51.0 (2.4)
SJCRH-13A	1991–94	≤ 18	165	76.9 (3.3)	88.1 (3.6)	70.4 (6.2)	60.9 (10.2)
TCCSG-L92-13	1992–95	≤ 15	347	63.4 (2.7)	67.8 (3.4)	56.7 (5.4)	59.3 (8.6)
UKALL-XI	1990–97	≤ 15	2090	63 (1.1)	74 (2.2)	59 (4.1)	51 (3.5)

AIEOP, Associazione Italiana di Ematologia ed Oncologia Pediatrica; BFM, Berlin-Frankfurt-Münster ALL Study Group; CCG, Children's Cancer Group; COALL, Cooperative ALL Study Group; DCLSG, Dutch Childhood Leukemia Study Group; DFCI, Dana Farber Cancer Institute ALL consortium; EORTC-CLCG, European Organisation for Research and Treatment of Cancer, Children's Leukaemia Cooperative Study Group; NOPHO, Nordic Society of Pediatric Hematology and Oncology; POG, Pediatric Oncology Group; SJCRH, St Jude Children's Research Hospital; TCCSG, Tokyo Children's Cancer Study Group; UKALL, UK Medical Research Council Working Party on Childhood Leukaemia; SE, standard error.

*Results were taken from a series of articles on longterm results of paediatric ALL clinical trials published by 12 major study groups or institutions (*Leukemia* 2000; 14: 2196–204).
†Standard-risk group included children 1–9 years old with leucocyte count < 50 x 10^9/L; high-risk patients are all others, except for infants. The basis for differences in 'overall' results was partly related to the disproportion of high-risk cases referred to some institutions.

Pathogenesis and molecular epidemiology

The precise pathogenetic events leading to the development of ALL are still unknown, but they are likely to affect genes that control lymphoid cell homoeostasis, resulting in dysregulated clonal expansion of immature progenitor cells. The prenatal origin of some leukaemias was established through genetic studies of identical twins with concordant leukaemia and backtracking of leukaemia-specific fusion-gene sequences (eg *MLL-AF4*, *TEL-AML1*) to neonatal blood spots.[10] The t(4;11) and *MLL-AF4* fusion sequence has a high concordance rate in identical twins (25–100%) and a very brief latency period (a few weeks to a few months), which suggests that this fusion per se may be sufficient for leukaemogenesis or, at the very least, may be able to provoke a secondary change leading to leukaemia development.[11] In other types of leukaemia, for example, those with the *TEL-AML1* fusion or T-cell phenotype, the concordance rate is lower, postnatal latency period is longer and variable, and clinical presentations and outcome of therapy may differ widely among identical twins. This feature suggests that a secondary postnatal molecular event is necessary for full leukaemic transformation.[11] Further insights were gained from a recent report of a triplet pregnancy in which the monozygotic twins developed concordant leukaemia with identical *TEL-AML1* fusion at 3 years of age, but the dizygotic co-twin did not have leukaemia or the fusion sequence.[12] The identical twins had, in addition to the fusion transcript, a secondary, independent deletion of the normal unrearranged TEL allele, suggesting a different postnatal event. Notably, the *TEL-AML1* fusion can be induced by stimulators of apoptosis in lymphoid cells[13] and is detected in blood of a high proportion of normal children with fever (~40%),[14] which provides further evidence that the fusion transcript per se is not enough to induce leukaemia.

Numerous epidemiological investigations have focused on infant leukaemias that involve the *MLL* gene, located at chromosome band 11q23.[15] *MLL* rearrangements are also common in therapy-related acute myeloid leukaemia (AML), arising shortly after treatment with topoisomerase II inhibitors (mainly epipodophyllotoxins).[16] The similarities between molecular genetic abnormalities in infant leukaemias and topoisomerase II inhibitor-related leukaemias suggest that transplacental fetal exposure to substances that inhibit topoisomerase II might be a critical event in the generation of leukaemias. Flavonoids (in food and drink), quinolone antibiotics, benzene metabolites, catechins, and oestrogens can all inhibit topoisomerase II, both *in vivo* and *in vitro*, and may cause mutations that lead to acute leukaemias with *MLL* rearrangements.[15] A recent case-control study disclosed significant associations between *in utero* exposure to DNA-damaging drugs, herbal medicines, and material pesticides, and the development of infant leukaemia with *MLL* rearrangements.[17] It is possible that the activity of enzymes that detoxify carcinogens may be low in infants with leukaemias or their mothers, since the functional doses from dietary and environmental exposures are much lower than those from anticancer chemotherapy. Indeed, quinones induce topoisomerase II-mediated DNA cleavage, and low activity of NAD(P)H (quinone oxidoreductase), an enzyme that converts benzoquinones to less toxic hydroxy metabolites, has been associated with infant leukaemias with the *MLL-AF4* fusions.[18] Genetic polymorphisms of other enzymes that detoxify carcinogens may also affect the risk of development of *de novo* leukaemias. In this regard, the deficiency of glutathione-S-transferases (GST-M1 and GST-T1), enzymes that detoxify electrophilic metabolites by catalysing their conjugation to glutathione, has been associated with infant leukaemias without *MLL*

rearrangement,[15] and ALL in black children.[19] Another recent study related *GST-M1* null and cytochrome P-450 CYP1A1*2A genotypes to an increased risk of childhood ALL; children carrying both genotypes were at greater risk.[20] Continued molecular epidemiological studies should provide further insights into the underlying mechanism(s) of leukaemogenesis in children and may lead to the development of effective preventive measures.

Risk assessment

Stringent evaluation of the risk of relapse at diagnosis is needed to direct therapy, so that patients are not over treated or under treated. Age, leucocyte count, leukaemic-cell genotype, and treatment response to early remission-induction therapy are commonly used in risk classification;[1–9] however, there has not been a consensus on the most useful criteria due to technical differences, feasibility, or both. Widespread agreement on the terminology for defining risk groups is also lacking. For example, patients were classified as lower risk, intermediate risk, or higher risk by the Children's Cancer Group;[2] standard risk, medium risk, or high risk by the Berlin-Frankfurt-Münster Consortium;[1] good risk B lineage, poor-risk B-lineage, or T-lineage by the Pediatric Oncology Group;[5] and standard risk, high risk, or very high risk at St Jude Children's Research Hospital. Having identified a group of patients at very low risk of relapse, the Children's Oncology Group recently proposed a four-group classification: low risk, standard risk, high risk, and very high risk.[21] In this review, we use the St Jude Children's Oncology Group risk classification. Infants of less than 12 months of age are generally treated on a separate protocol.

The type of treatment programme is the most important determinant of outcome. Thus, clinical and biological variables may lose their predictive strength when treatment is changed. Until now, age at presentation and leucocyte count have been strong prognostic indicators in B-lineage but not T-lineage ALL.[5,6,8] Even in B-lineage ALL, their value is limited because up to a third of the so-called standard-risk patients (age 1–9 years with leucocyte count $< 50 \times 10^9$/L) may relapse (Table 1), and patients at very high risk, who require allogeneic heamopoietic stem-cell transplantation, cannot be reliably distinguished from the high-risk cases by these measurements. For reasons still poorly understood, boys fare significantly worse than girls on most treatment protocols,[1–8,22] with rare exceptions.[9] In the studies of the US collaborative group, African-Americans and children of Hispanic origin had a significantly worse outcome than white children, after adjustment for other prognostic features.[23] By contrast, African-Americans fared as well as white children in our single institution protocols, a finding we attributed to equal access to effective contemporary treatment for both groups of patients.[24]

Primary genetic abnormalities of leukaemic cells influence disease aggressiveness and response to therapy, but are not 100% predictive of outcome. For example, up to 20% of children with favourable genetic features (*TEL-AML1* fusion and hyperdiploidy > 50 chromosomes) will eventually relapse, although a third of those with high-risk abnormalities (the Philadelphia chromosome with *BCR-ABL* fusion and the t(4;11) with *MLL-AF4* fusion) can be cured with chemotherapy alone.[25] Age 1–9 years conferred a favorable prognosis in cases with Philadelphia chromosome or the t(4;11), and high leucocyte count was also associated with a poor outcome in those with the former genetic feature.[21,26] More recently, the presence of trisomies 4, 10, and 17 has been associated with a very favourable prognosis;[2,5] this finding warrants further mechanistic investigation and independent confirmation. The mechanism by which genetic abnormalities result in differences in disease aggressiveness or drug sensitivity are only partially explained. In the case of hyperdiploid ALL (> 50 chromosomes), however, leukaemic cells have a distinct propensity to undergo apoptosis, accumulate higher concentrations of methotrexate polyglutamates, and are more sensitive to methotrexate and mercaptopurine *in vitro*.[27] These features may well explain the low leukaemic-cell counts at diagnosis and the good response to therapy typical of these cases.

One plausible reason for the unpredictable relation between biological features of leukaemic cells and response to therapy is that pharmacodynamic and pharmacogenomic factors can exert a crucial influence on the effectiveness of treatment.[28] There are wide variations in the rate of metabolism and systemic clearance of antileukaemic agents and in the absorption of orally administered chemotherapy. Low systemic exposure to methotrexate and low dose intensity of mercaptopurine have each been associated with a poor treatment outcome.[29,30] This finding indicates that treatment is unsuccessful in some patients because they have received inadequate doses of drugs, and not because their leukaemia is drug-resistant. In support of this, we recently reported that concomitant administration of anticonvulsants which induce cytochrome P450 (phenytoin, phenobarbital, carbamazepine, or a combination) significantly increases the systemic clearance of several antileukaemic agents and is associated with lower chemotherapeutic efficacy.[31] We now use other anticonvulsants (eg gabapentin and valproic acid) which are less likely to induce the activity of drug-metabolising enzymes. Genetic polymorphisms of several drug-metabolising enzymes are also associated with treatment outcome. We have shown that patients who have homozygous or heterozygous deficiency of thiopurine methyltransferase, the enzyme that catalyses the S-methylation (inactivation) of mercaptopurine, tended to have better event-free survival, probably because they had received higher dose intensity of mercaptopurine.[30] However, the thiopurine methyltransferase genetic polymorphism is also linked to acute dose-limiting toxic effects,[32] and the risk of irradiation-induced brain tumour[33] and therapy-related acute myeloid leukaemia,[16,34] in the context of antimetabolite-based therapy. Therapy must therefore be adjusted in patients with homozygous mutant genotypes of this enzyme and in many heterozygotes. The null genotype (absence of both alleles) for *GSTM1* or *GSTT1* and the *GSTP1 Val105/Val105* genes have also been associated with a lower risk of relapse, perhaps because

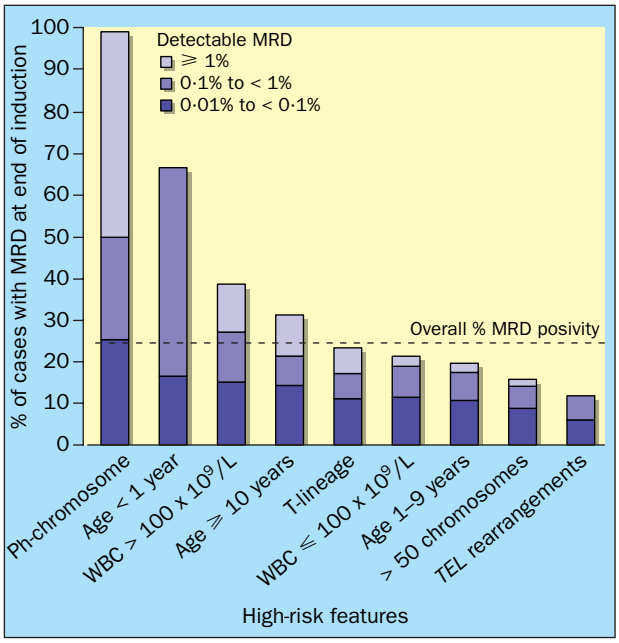

Figure 2. Proportion of cases with detectable minimal residual leukaemia and the degree of positivity at the end of remission induction, assessed by presenting clinical and biological features. Patients with high-risk features, such as Philadelphia chromosomes, age < 1 year or ⩾ 10 years, and leucocyte count ⩾ 100 x 10⁹/L, are more likely to have detectable residual leukaemia. They also tend to have higher levels of positivity.

of the reduction in detoxification of cytotoxic chemotherapy.[35]

Since response to therapy is determined by many factors,[25] measurements of this response *in vivo* should have a better prognostic strength than that of any other individual biological or host-related feature. The independent prognostic importance of a patient's gross early response to therapy (ie initial decrease in leukaemic blasts) has been recognised by investigators of the Children's Cancer Group and the Berlin-Frankfurt-Münster consortium since the early 1980s. They assessed the response by morphological examination of the bone marrow or peripheral blood. Although their methods can be readily applied at any centre, neither measure has great precision, because about 20% of patients with a good initial response eventually relapse, and a third of patients with a poor response may survive long term, when treated with intensive chemotherapy alone.[1,2]

Measurements of minimal residual disease (MRD), by flow-cytometric detection of aberrant immunophenotype or analysis by polymerase chain reaction (PCR) of clonal antigen-receptor gene rearrangements, afford a level of sensitivity and specificity that cannot be attained by traditional morphological assessment of treatment response.[36–38] Patients who achieve an immunological or molecular remission, defined as leukaemic involvement of less than 10^{-4} nucleated bone-marrow cells on completion of induction therapy, have a much more favourable prognosis than those who do not achieve this status. Patients who are in morphological remission but have a post-induction MRD level of 1% of more, fare as poorly as those who do not achieve clinical remission by conventional criteria (⩾ 5% blast cells).[36–38] About half of all patients show a disease reduction to 10^{-4} or lower after only 2 weeks of remission induction, and they appear to have an exceptionally good treatment outcome.[39,40] Although MRD positivity is strongly associated with known presenting risk features (Figure 2), it has independent prognostic strength (Figure 3).[41] Sequential monitoring of MRD can improve the precision of risk assessment still further. Thus, the persistence of MRD (⩾ 0.01%) beyond 4 months from diagnosis was associated with an estimated 70% cumulative risk of relapse.[36,38] Patients with 0.1% MRD or more at 4 months had an especially dismal outcome.[36] We have therefore incorporated MRD detection into our current risk-classification system (Figure 4).

One prerequisite for the clinical application of MRD detection is the ability to study all patients. The success rate of PCR analysis of antigen-receptor genes ranges from 80 to 90% because sufficiently specific leukaemia sequences are lacking in the remaining patients. Comparative analyses of gene expression in normal B-cell progenitors and B-lineage leukaemic cells have identified new leukaemic-associated markers (eg CD58), boosting the cases that can be studied by flow cytometry to 90%.[42] Tandem application of flow cytometry and PCR testing has allowed us to study MRD successfully in more than 100 consecutive cases.[40]

Treatment

The recently improved cure rate of ALL can be attributed mainly to the development of more effective chemotherapeutic regimens through successive well-designed clinical trials. In patients with mature B-cell ALL, short-term (2–8 months) regimens of intensive chemotherapy primarily based on cyclophosphamide, methotrexate, cytarabine, and intrathecal therapy, currently result in cure rates of 74–87%.[43,44] Recent development of a highly effective uricocytic agent, recombinant urate oxidase, promises to improve treatment still further by reducing early morbidity and mortality from tumour lysis syndrome and acute renal failure.[45]

Infant ALL, especially in patients with *11q23/MLL* rearrangements, remains one of the most difficult therapeutic challenges. Various treatment regimens have been tested in infants, generally resulting in event-free survival of 20–35%.[15] In several recent clinical trials, high-dose cytarabine, high-dose methotrexate, and intensive consolidation/reinduction therapy seemed to improve outcome.[46,47] However, these results should be viewed as preliminary because of the small numbers of patients studied, the lack of randomisation, and the disproportionate number of cases with high-risk disease (ie *11q23/MLL* rearrangements). Intensive systemic and intrathecal treatments, without cranial irradiation, seem to provide adequate protection of the central nervous system (CNS), even in infants with CNS leukaemia at diagnosis.[48] Most investigators now treat infants as a unique subgroup with multiple drugs given at high doses, without cranial irradiation.

For all other patients, the basic approach to therapy consists of a brief remission-induction phase, followed by intensification (consolidation) therapy, and then long-term continuation treatment. All patients require treatment for

subclinical leukaemia of the CNS, which should be initiated early in the form of intrathecal therapy.

Remission induction

The first goal of therapy is to induce complete remission with restoration of normal hemopoiesis. The induction regimen invariably includes a glucocorticoid (prednisone, prednisolone, or dexamethasone), vincristine, and at least one other agent (asparaginase or an anthracycline). With improvement in supportive care and chemotherapy, the rate of complete remission now ranges from 96% to 99%.[1–9] Attempts have been made to intensify induction therapy, especially in high-risk and very-high-risk disease, on the premise that a more rapid and profound reduction of the leukaemic-cell burden may forestall the development of drug resistance in leukaemic cells. However, several studies have suggested that intensive induction therapy may not be necessary, provided that patients receive postinduction intensification therapy.[2,3] Moreover, intensive induction therapy may lead to a poor overall outcome due to an increase in early morbidity and mortality.[49,50] It is relevant that we found that patients who achieve an immunological or molecular remission at week 14 after remission induction have a low risk of relapse, similar to those who attain such remission status earlier (ie on completion of remission induction).[41]

Most remission induction regimens include colaspase. However, several clinical trials using this drug alone in the post-induction period had an excellent remission-induction rate with low morbidity (especially in terms of thrombotic complications), and excellent long-term event-free survival.[3,9] A recent randomised trial compared the relative efficacy and toxicity of colaspase and epirubicin as a third remission-induction agent in patients with standard risk ALL. Patients treated with colaspase had a significantly lower rate of successful remission induction owing to a higher rate of fatal infection.[49] Hence, although colaspase is an indispensable agent in the treatment of ALL, its use in remission-induction regimens is being challenged. Furthermore, different forms of asparaginase have different pharmacokinetic profiles and efficacy.[25,49]

Perhaps because it has better penetration into cerebrospinal fluid and a longer half-life, dexamethasone has been used instead of prednisone or prednisolone in some induction and continuation regimens.[25] Although this substitution improved outcome in one randomised trial,[2] it was also implicated as a cause of excessive life-threatening infections and septic deaths in another study.[50] This finding underscores the importance of potential drug interactions in any complex multiagent regimen.

Intensification (consolidation) therapy

With restoration of normal haemopoiesis, patients in remission become candidates for intensification (consolidation) therapy. The importance of this phase of therapy is not disputed, but there is no consensus on the best regimens and their duration. Delayed intensification (or reinduction), pioneered by investigators in the Berlin-Frankfurt-Münster consortium, is perhaps the most widely used regimen. It is basically a repetition of the initial

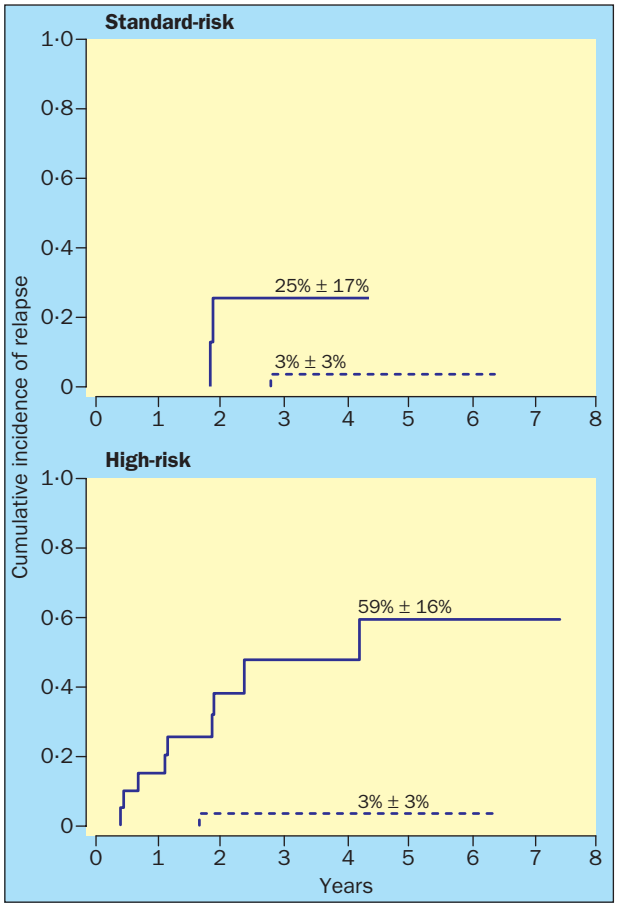

Figure 3. Cumulative incidence of relapse in children with standard-risk (top) and high-risk (bottom) ALL classified by minimal residual disease (MRD) status at the end of remission induction. A total of 52 patients were classified as standard-risk, 8 of who were MRD-positive (blue line) and 44 of who were MRD-negative (green line) ($p = 0.0096$). Of the 54 high-risk patients, 20 were MRD-positive (blue line) and 34 were MRD-negative (green line) ($p < 0.001$). Patients were treated on Total Therapy Study XIII at St Jude Children's Research Hospital (ref 41) Standard-risk ALL was defined by the presence of favorable genetic features (TEL-AML1 fusion or hyperdiploidy > 50 chromosomes) and high-risk by the presenting leucocyte count ⩾ 50 x 109/L or age ⩾ 10 years. All patients were in complete morphological remission at the time of MRD studies. MRD positivity is defined as ⩾ 0.01% of mononuclear cells expressing leukaemia-specific immunophenotypes in bone marrow.

induction therapy at 3 months after remission, and is most beneficial for standard-risk cases. Investigators at the Children's Cancer Group showed that double delayed intensification started at week 32 of treatment improved outcome of patients with high-risk (or so-called intermediate-risk) leukaemia.[51] Of interest in this study, additional pulses of vincristine and prednisone during continuation therapy did not improve outcome, suggesting that the benefit of double delayed intensification was due to increased dose intensity of other agents such as colaspase, anthracycline, cytarabine, and cyclophosphamide, or due to the timing or scheduling of the intensification regimen. Extended and stronger intensification therapy also significantly benefited patients with high-risk ALL and a slow response to initial induction therapy.[52] Whether this approach will benefit standard-risk cases remains uncertain. Hence, reinduction or delayed-intensification

therapy seems to be beneficial to all patients, and double or prolonged intensification seems to be beneficial to those with high-risk or very-high-risk leukaemia.

The use of different intensification regimens in various clinical trials has also led to the identification of effective treatment components for certain subtypes of leukaemia. For example, improved outcome of T-lineage ALL in the clinical trials of the Dana-Farber Cancer Institute consortium and Children's Cancer Group has been credited to the intensive use of colaspase (Table 1),[2,9] a finding which has been corroborated by a randomised study of the Pediatric Oncology Group.[53] Interestingly, in the study of the Dana-Farber Cancer Institute consortium, patients who tolerated at least 26 weekly doses of asparaginase had a significantly better outcome than those who received fewer doses.[9]

Intensive asparaginase treatment is also credited with a very low rate of relapse among *TEL-AML1*-positive cases treated on the protocols of Dana-Farber Institute corsortium.[9] In line with this clinical observation, leukaemic blast cells with the *TEL-AML1* fusion are reportedly highly sensitive to asparaginase *in vitro*.[54]

Very high doses of methotrexate (5 g/m^2) also seem to improve outcome in patients with T-lineage ALL.[1,21] This observation is consistent with our finding that T-lineage blast cells accumulate methotrexate polyglutamates (active metabolites of methotrexate) less avidly than do B-lineage blast cells, so that higher serum concentrations of methotrexate are needed for adequate response in T-lineage ALL.[55] Nonetheless, high-dose methotrexate (but not intravenous mercaptopurine) also benefits patients with B-lineage ALL;[56] the optimum dose of methotrexate for individual genetic subtypes remains to be determined, but a dose of 2.5 g/m^2 should be adequate for most of these patients.[29]

The most successful postremission intensification regimens generally feature continuous therapy,[9,52] whereas high-dose pulse therapy with long rest periods due to myelosuppression appears to be less effective.[57] This observation is consistent with the concept of metronomic dosing for solid tumours, based on the idea that continuous or frequent administration of cytotoxic drugs may improve outcome by abrogating the ability of slowly proliferating endothelial cells, essential for tumour-cell survival, to repair and recover during the usual rest periods.[58] Angiogenesis has also been seen in ALL,[59] and chemotherapy could affect the recovery of bone-marrow mesenchymal and endothelial cells that provide essential survival factors for leukaemic lymphoblasts.[60]

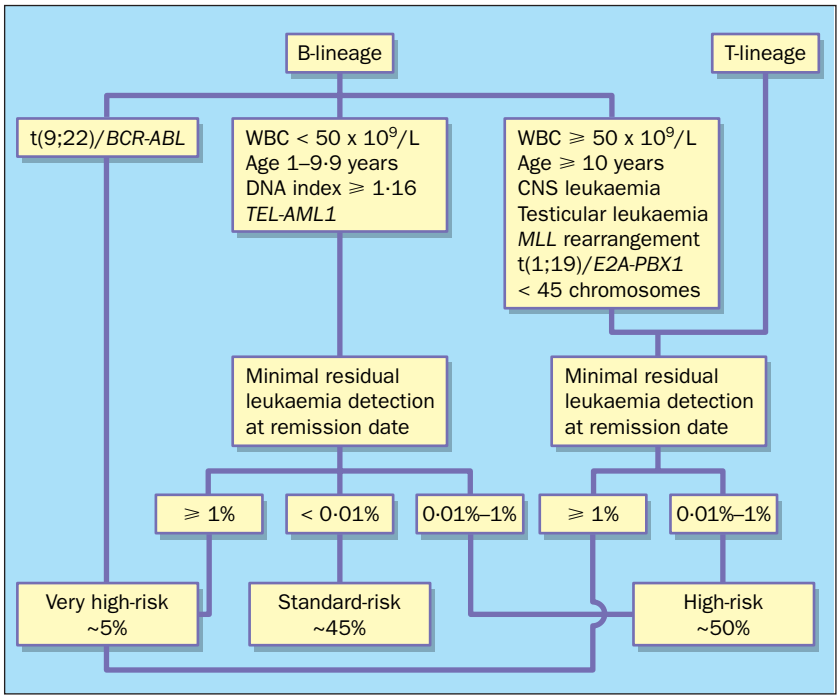

Figure 4. Risk classification scheme in Total Therapy Study XV at St Jude Children's Research Hospital. Infants 12 months old or less are treated in a separate protocol. Any patient who does not achieve morphological remission after completion of induction therapy, or who has 0.1% or more residual leukaemia 4 months after remission induction, is considered to have very high-risk leukaemia. Estimated proportions of patients classified to each of the three risk groups are shown in their respective boxes.

Continuation treatment

For reasons that are poorly understood, children with ALL (except those with mature B-cell leukaemia) require long-term continuation treatment. In a recent study, the attempt to intensify early therapy, but shorten total treatment duration to 1 year, resulted in poor overall event-free survival.[7] Interestingly, the shorter therapy seemed to be adequate for a small subset of children with T-cell disease who responded well to prednisolone. Notwithstanding this result, the general rule is to continue therapy for a total duration of 2.0–2.5 years. Many investigators prefer to extend treatment for boys to 3 years because of their generally poorer outcome compared with girls,[22] although the benefit of this approach remains to be determined.

The combination of methotrexate given weekly and mercaptopurine given daily constitutes the standard 'backbone' of ALL continuation regimens. Tailoring of doses to the limits of tolerance (as indicated by low neutrophil counts) has been associated with better clinical outcome.[61] However, overzealous use of mercaptopurine, so that neutropenia precludes further use of chemotherapy and reduces overall dose intensity, is counterproductive.[30] It is well recognised that the rare patients (one in 300) with an inherited deficiency of thiopurine-S-methyltransferase have extreme sensitivity to mercaptopurine. We recently showed that the 10% of patients who are heterozygous for this deficiency, and thus have intermediate levels of enzyme activity, may also require dose reduction, albeit moderately, to avert side-effects.[30] Identification of the

genetic basis of this autosomal codominant trait has made possible the molecular diagnosis of these cases.[62] Studies can now be done in patients who have poor tolerance to methotrexate and mercaptopurine, to identify and selectively lower the dose of the responsible agent, allowing full doses of the other drug.

The addition of intermittent pulses of vincristine and a glucocorticoid to the antimetabolite continuation regimen improves results[63] and has been widely adopted. Dexamethasone has been substituted for prednisone during continuation therapy in many clinical trials, because of its better clinical efficacy.[2] However, studies are needed to find the optimum dose and duration of dexamethasone therapy during this phase of treatment.

Subclinical treatment of CNS

Several factors affect the control of leukaemia in the CNS: presenting risk features, the amount of leukaemia blasts cells in the cerebrospinal fluid, and the type of systemic and CNS-directed therapy. Patients with high-risk genetic features, large leukaemic-cell burden, T-lineage ALL, and leukaemic cells in the cerebrospinal fluid (even from iatrogenic introduction from a traumatic lumbar puncture), are at increased risk of CNS relapse and require more intensive CNS-directed therapy.[64] High-dose methotrexate, although useful for preventing haematological or testicular relapse, generally has only a marginal effect on the control of CNS leukaemia. However, in one study, high-dose methotrexate plus intrathecal methotrexate reduced the risk of CNS relapse but did not affect other relapses or overall surviva1.[8] Additional analyses of the method of high-dose methotrexate and folinic acid delivery are needed to explain this finding. By contrast, dexamethasone was definitely shown to improve CNS control.[2] The efficacy of triple intrathecal therapy with methotrexate, hydrocortisone, and cytarabine, compared with that of intrathecal methotrexate alone, is still unknown and is the subject of a current randomised trial of the Children's Cancer Group.

Cranial irradiation is the most effective CNS-directed therapy. However, the concern that it can cause substantial neurotoxicity and occasional brain tumours, has prompted most leukaemia therapists to use intensive intrathecal and systemic chemotherapy for 80–90% of patients. This approach, in combination with cranial irradiation for selected high-risk or very-high-risk cases, has lowered the CNS relapse rate to less than 5% in most studies.[9,52,57,65] Radiation dose can be lowered to 12 Gy without increasing the risk of CNS relapse, provided effective systemic chemotherapy is used.[57] Whether CNS irradiation can decrease the risk of haematological relapse is controversial. In one study, the omission of cranial irradiation was implicated as a cause of increased CNS and haematological relapse in T-lineage ALL with presenting leucocyte count of more than 100 X 10^9/L.[66] However, the study involved only a small number of cases, and inadequate systemic chemotherapy might have contributed to the increased rate of relapse. In a recent retrospective study of T-lineage ALL with high presenting leucocyte count (> 50 X 10^9/L) or CNS leukaemia at diagnosis, CNS irradiation reduced the rate of relapse CNS, but did not improve event-free survival.[67]

Two other studies omitted cranial irradiation altogether for all patients.[4,68] The cumulative risks of isolated CNS relapse were 4.2% and 3.0%, and rates of any CNS relapse (including combined CNS and haematological relapse) were 8.3% and 6.0%, respectively. Patients with CD10-negative B-lineage (pro-B) phenotype, CNS 2 or CNS 3 status, and a leucocyte count of greater than 100 X 10^9/L had an increased risk of CNS relapse.[4,68] Since the overall 8-year event survival rates for the two studies were only 60.7% (SE 4.0%) and 68.4 (SE 1.2%), whether improved systemic chemotherapy can reduce the CNS relapse hazard is still unclear. Moreover, patients with isolated CNS relapse who had not received cranial irradiation as initial CNS-directed therapy, have a very high retrieval rate; in those who had a long initial remission before the CNS event, the long-term prognosis may even be similar to that of newly diagnosed patients.[69] Therefore, we and Dutch investigators are testing the hypothesis that, in the context of intensive systemic and intrathecal therapy, cranial irradiation can be omitted altogether, irrespective of a patient's risk features. Cranial irradiation is now reserved for salvage therapy, thus sparing most patients from its toxic effects. While this approach is under study, most clinical trials still specify cranial irradiation for patients at particularly high risk of CNS relapse, eg those with CNS 3 status or T-cell with high leucocyte count.

Allogeneic haemopoietic stem-cell transplantation

Many advances have been made in transplantation, such as prevention of graft-versus-host disease, expansion of the pool of suitable unrelated or related donors, acceleration of engraftment, enhancement of the graft-versus-leukaemia effect, and supportive care. Such topics are beyond the scope of this review. Because improvements in transplantation and chemotherapy are occurring in parallel, the indications for transplantation in newly diagnosed and relapsed patients should be subjected to periodic re-evaluation. At present, Philadelphia-chromosome-positive ALL and early haematological relapse are clear indications for transplantation.[25,26] However, transplantation has not been shown to improve outcome in other types of very high-risk leukaemia, including infant ALL with MLL rearrangement (Pui CH, unpublished observation).

Late effects

Treatment protocols have changed over time and so has the range of late therapy-related sequelae. Most protocols avoid the use of regimens that can induce second cancers and emphasise the use of other drugs, such as glucocorticoids, antimetabolites, and asparaginase. Increasing use of glucocorticoids during reinduction and continuation therapy has been associated with an increase in the occurrence of osteonecrosis. This complication is more common in older children (≥ 10 years), female patients, and white children (compared with African-Americans).[70]

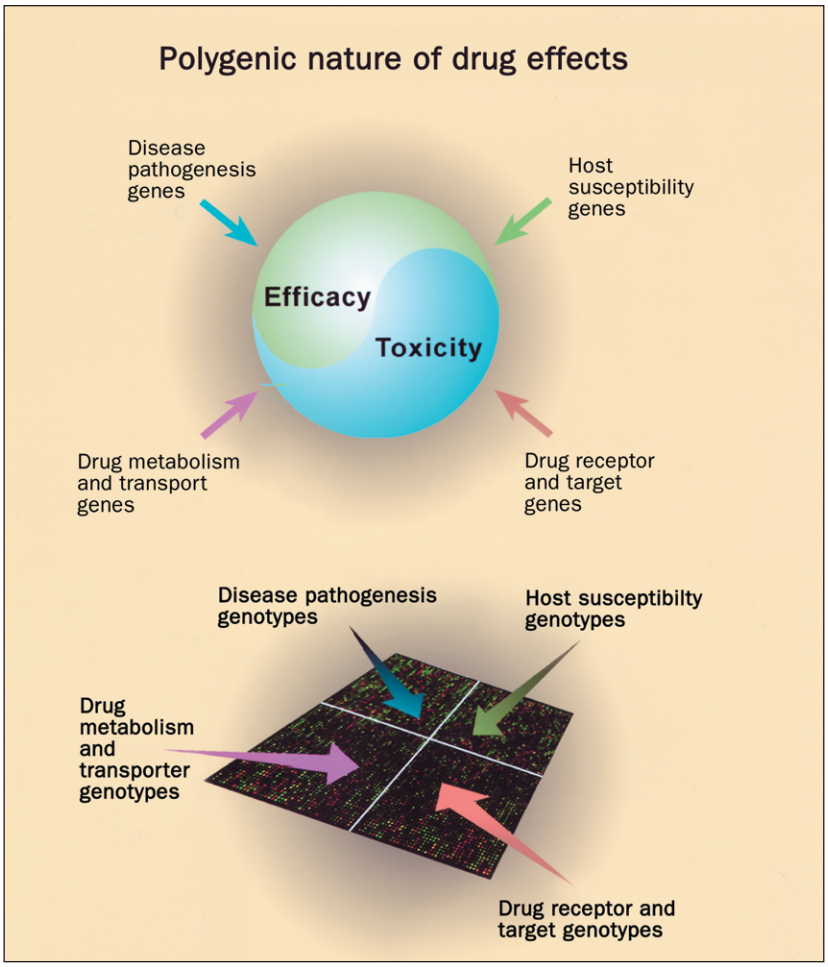

Figure 5. Inherited differences in most drug effects are polygenic in nature, with polymorphisms in several genes underlying interperson differences in drug efficacy or toxicity (top panel). Once these pharmacogenomic relationships are elucidated, it will be possible to develop molecular diagnostics (eg oligonucleotide microarray assay) that can be used to optimise the choice and dosage of antileukaemic therapy (bottom panel). Such genetic diagnostics will then be used along with molecular diagnostic of genetic abnormalities in the leukaemia cells, to tailor therapeutic strategies to the genetics of the host and the leukaemia.

The increased risk in female patients may be related to their early pubertal development, because maturing bones (with epiphyseal closure and reduced intramedullary blood flow) are more susceptible to this complication. Factors contributing to the ethnic difference are unknown. We and others have recently decreased the duration of dexamethasone therapy because the preliminary result of the Children's Cancer Group indicated that intermittent use of dexamethasone would reduce the risk of this complication.[21] Prospective monitoring and early intervention could also prevent the development of debilitating complications. Indeed, some of the early osteonecrotic changes are reversible with proper management, including physiotherapy (Pui CH, unpublished observation).

Another form of bony abnormality is decreased bone mineral density, which has been attributed to cranial irradiation and intensive systemic chemotherapy, especially regimens including high-dose antimetabolites or glucocorticoids. We found that white patients are most likely to have low bone mineral density.[71] Continuing studies are investigating whether genetic polymorphisms of the vitamin D receptor influence the severity of low bone mineral density. Although treatment of low bone mineral density should reduce the risk of osteoporosis and fractures later in life, intervention studies are needed to find the optimum therapy (eg nutritional counselling, exercise, vitamin D, phosphate or calcium supplement, or bisphosphonates).

Thrombotic complications, half of which were cerebral venous thromboses, occurred in as many as 11% of patients receiving remission induction or reinduction with a glucocorticoid, vincristine, and asparaginase.[72] This high frequency of thrombotic complications is undoubtedly due to the increased use of asparaginase and frequent placement of a central line, as well as improved diagnostic imaging and heightened awareness. German investigators found that 27 of their 32 patients with thrombotic complications had one or more inherited prothrombotic defects.[72] In fact, half of the patients with a prothrombotic defect developed thrombosis. If confirmed, this finding would pave the way for effective prophylaxis.

CNS-directed therapy without cranial irradiation has been associated with adverse cognitive and academic late effects, particularly for girls.[73] In one study, visual and verbal short-term memory deficiencies were observed in children who had received about 20 triple intrathecal treatments with methotrexate, hydrocortisone, and cytarabine over 3 years, as the sole CNS-directed therapy (without intravenous methotrexate).[73] Clearly, neuropsychological function should be assessed in survivors of childhood ALL, and appropriate remediation programs should be developed to address specific cognitive impairments.

Future directions

Recent emphasis has been placed on the study of genetic polymorphisms in drug-metabolising enzymes, drug transporters, and targets of drug action[28] (Figure 5). The information should be useful for optimising drug doses (especially those with a low therapeutic index) and drug combinations (to increase antileukaemic effects and to reduce late sequelae). Efforts are also being made to identify new antileukaemic drugs and new approaches to therapy. Identification of specific oncoproteins and understanding of the molecular processes regulating

Search strategy and selection criteria
Published data for this review were identified by searches of MEDLINE and other bibliographic information available in the PubMed database. The search terms ëAcute lymphoblastic leukaemia', were used. References from relevant articles and abstracts from recent international conferences were also included. We also contacted researchers for unpublished data. Additional papers were identified from the personal collections of the authors. Only papers published in English after 1990 were used.

leukaemic-cell survival and apoptosis have paved the way for therapy directed to pivotal molecular targets.[21] Of the new agents being tested, GW-506U78 (a prodrug of arabinosylguanine) is particularly effective in patients with T-lineage ALL but is associated with significant neurological toxic effects.[25] STI-571 (known as Gleevec) selectively inhibits BCR-ABL tyrosine kinase, leading to growth inhibition and apoptosis of leukaemic cells with this fusion product. In a recent study, this agent induced a response rate of 70%, with 20% complete (albeit transient) responses in patients with BCR-ABL-positive ALL in relapse, or chronic myeloid leukaemia in lymphoid blast crisis.[74] Whether or not ST1-571 will improve outcome in patients with newly diagnosed BCR-ABL-positive ALL remains to be determined. Other promising agents include antibodies conjugated to toxins, eliciting complement activation and cell cytoxicity, or triggering signals that inhibit cell growth;[21] molecular agents that increase the susceptibility of leukaemic cells to apoptosis, such as BCL2 antisense oligonucleotides and proteasome inhibitors;[21] and, genetically manipulated cytokines that induce apoptosis in ALL cells.[75]

As new information continues to emerge from the Human Genome Project, DNA microarray studies, high-throughput DNA and protein screening systems, and from advances in bioinformatics, one can look forward to accelerated progress in leukaemia research. Ultimately, such progress should result in improvement of the clinical management and cure rates of childhood ALL – a disease that has long been an example of a disseminated cancer that is curable with chemotherapy.

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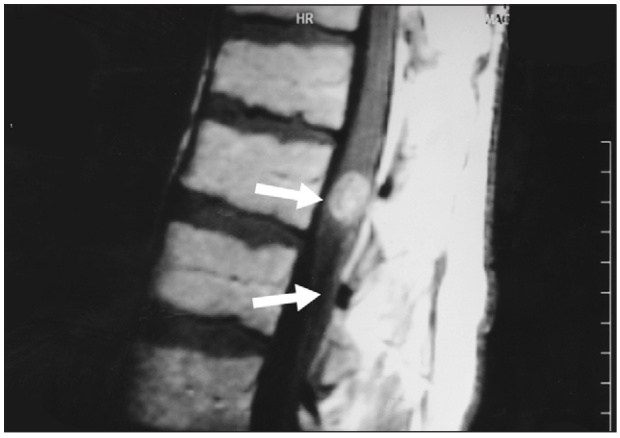
A list of references for further reading appears on *The Lancet Oncology*'s website: www.oncology.thelancet.com

Clinical picture

Intramedullary spinal cord metastasis

A 69-year-old man initially presented with inoperable non-small-cell lung cancer. He received 4 cycles of palliative chemotherapy with mitomycin, vinblastine, and cisplatin (MVP) chemotherapy with an objective partial response and improvement in symptom control. On deterioration of his condition, he received palliative thoracic radiotherapy. He subsequently developed lower limb paraplegia. Examination confirmed mild pyramidal weakness with hyporeflexia and an absent plantar response. Pinprick sensation was reduced below the T10 dermatome and a large bladder was palpable. He was diagnosed with spinal cord compression and given high-dose dexamethasone. A gadolinium-enhanced MRI scan revealed a 1.7 cm enhancing intramedullary mass at the level of the T12 vertebra (top arrow). There was an associated syrinx extending up the thoracic cord (bottom arrow).



The patient was treated with a course of palliative radiotherapy and regained some motor function. He was, however, largely confined to a wheelchair and required an indwelling catheter. He was discharged after 2 weeks of in-patient care, to be followed up in the out-patient department.

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