

## RECENT ADVANCES

## Recent advances in management of acute leukaemia

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**Abstract**

**There have been significant improvements in the outlook for children with acute leukaemia but these advances are only available to a minority of the world's children. There is still room for improvements in conventional chemotherapy and these need evaluation in randomised trials. The role of bone marrow transplants in first remission is evolving as chemotherapy becomes more effective. New treatments are needed for relapsed patients. Molecular diagnosis has refined the assessment of prognosis but the extra value afforded by measurement of minimal residual disease is not clear. International collaboration is needed to evaluate treatment for rare subtypes of leukaemia.**

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In the last decade the lessons learned about the biology of acute leukaemia have begun to have an impact on the management of patients. The outlook for children with acute lymphoblastic leukaemia (ALL) has improved steadily so that now at least 60–70% of children achieve long term survival and cure. Recent improvements in the rarer acute myeloid leukaemia (AML) have nudged survival rates to about 50%. High dose therapy and bone marrow transplantation (BMT) have become safer and more readily available but treatment for children who relapse remains unsatisfactory.

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Table 1 Cytogenetic findings in acute leukaemia

Abnormality	Frequency (% ALL or AML)	Clinical features
<i>Lymphoblastic leukaemia</i>		
High hyperdiploidy	25–35%	Common ALL, good prognosis
Hypodiploidy	5–8%	Poor prognosis
t(9;22)—Ph <sup>+</sup> chromosome	2–3%	Poor prognosis
t(12;21)	16–22%	Common ALL, probably good prognosis
t(1;19)	5%	Average prognosis
t(4;11) other 11q23	5–8%	Infant ALL, poor prognosis
t(8;14)	1–2%	B-ALL
14q11, 7q35, 7p15	1–2%	All associated with T-ALL
<i>Myeloid leukaemia</i>		
t(8;21)	10–15%	Good prognosis
t(15;17)	8–15%	Hypergranular promyelocytic leukaemia, good prognosis
Inv16	6%	Good prognosis
Monosomy 7	5–7%	Poor prognosis
t(9;11) other 11q23	8–10%	Young age, monocytic leukaemia

**The biology of acute leukaemia**

Leukaemia is a clonal disease resulting from genetic mutations and transformation of a single early progenitor myeloid or lymphoid cell. Despite much research the causes of acute leukaemia remain largely unknown.<sup>1</sup> It is postulated that the common form of lymphoblastic leukaemia starts with a change in proliferating early B cells in utero but requires subsequent genetic damage, perhaps associated with an unusual response to infection.<sup>2</sup>

Leukaemic cells may be classified by the use of monoclonal antibodies and, in ALL, have the surface antigen profile of either early B or T lymphoid cells. The cells are also characterised by a number of non-random genetic abnormalities. The most well known of these is the Philadelphia chromosome—a translocation between chromosomes 9 and 22 (t9;22) which was first described in chronic granulocytic leukaemia, but now known to occur in 1–2% of children with ALL and more than 20% of adults with ALL.<sup>3</sup>

Cytogenetic changes in acute leukaemia were first identified by routine banding techniques, but the advent of fluorescent in situ hybridisation and molecular techniques has allowed more sensitive and specific analysis of genetic abnormalities.<sup>4</sup> It has become apparent that the most common cytogenetic change in ALL is a cryptic translocation t(12;21), which cannot be detected on routine cytogenetic analysis. Immunological and cytogenetic investigation of leukaemias has, in addition to biological insights, proved extremely helpful both in diagnosis and risk assessment. Table 1 lists some of the most common non-random cytogenetic changes in acute leukaemia, in many of which the precise genetic alterations have been identified.<sup>4</sup>

Both immunological and molecular techniques have also been used to measure minimal residual disease (MRD). The conventional bone marrow examination, used to assess haematological remission, can only detect at best 3–5% leukaemic blasts in an otherwise normal bone marrow. Immunological techniques for measurement of MRD rely on the presence of aberrant combinations of antigens on the cell surface. Such combinations are present in about 60% of acute leukaemias and can probably detect about one in 10<sup>-4</sup> cells. The polymerase chain reaction allows amplification of RNA or DNA from leukaemic cells with

non-random genetic abnormalities such as those in table 1 and can detect up to one in  $10^{-5}$  cells. Many cases of ALL lack one of these genetic abnormalities but it is possible to establish a clonal marker by examination of the pattern of T cell and immunoglobulin gene receptor rearrangements in the diagnostic sample. This "patient specific" marker can then be used to evaluate residual disease on follow up. It has been shown that persistent MRD in patients who have received several months of treatment is associated with an increased risk of relapse.<sup>5</sup> Studies are now in progress to assess how best to use these techniques to refine treatment, and whether they add much additional information to other measures of response to treatment, such as speed of clearance of blast cells from blood or marrow.<sup>6</sup>

#### Improvements in supportive care

A small but important contributory factor to improved survival in lymphoblastic leukaemia is the reduction in treatment related mortality which has been achieved by improved supportive care. The most important measure is prompt investigation and treatment of possible bacterial or fungal infections in severely neutropenic patients.<sup>7</sup> The improved uptake of measles immunisation in the UK has led to a reduction in deaths from this devastating complication of continuing (maintenance) treatment which it is hoped will be sustained. Modern treatment for AML is associated with high short term toxicity, but the mortality rate halved in the latter part of the recent AML10 trial, presumably with improved management of bacterial and fungal infections.<sup>8</sup>

#### ROLE OF THE SHARED CARE CENTRE

It is appropriate for all children with leukaemia to be referred to a tertiary centre for diagnosis, risk assessment, and treatment planning. The more intensive phases of treatment should normally be carried out at the tertiary centre. Continuing (maintenance) therapy remains an important part of treatment of lymphoblastic leukaemia and, with appropriate guidelines, lends itself to shared care, the level of which should be a matter for local negotiation. The document on Standards of Care for Children with Leukaemia, published by the Royal College of Pathologists (1996), outlined standards for both specialist and shared care centres and forms a useful basis for future moves towards standard setting and accreditation.

#### Acute lymphoblastic leukaemia

The standard "backbone" of treatment for ALL has remained unchanged for over 25 years and includes remission induction, treatment to prevent overt leukaemic infiltration of the central nervous system (CNS directed therapy), and a period of outpatient based continuing (maintenance) therapy. The steady improvement in survival of children with ALL is a result of a number of modifications of this treatment, the value of which have been confirmed by randomised clinical trials.

#### INDUCTION AND INTENSIFICATION

Over 95% of children with ALL achieve remission after three to four weeks of treatment with oral steroids, weekly intravenous vincristine, and a third drug, usually L-asparaginase. Large prospective randomised trials, conducted in both Europe and North America have shown that giving one or more courses of intensified chemotherapy during the first eight to 10 months from diagnosis significantly reduces the risk of relapse.<sup>9,10</sup> This treatment appears to benefit all children with ALL, including those whose clinical features suggest a good chance of cure. There is wide variation between protocols in the choice of drugs, the dose intensity, and the timing of intensification treatments. The German Berlin-Frankfurt-Munster collaborative group first pioneered prolonged lower dose induction/intensification given over four to six weeks<sup>11</sup>; this has also been used in large randomised studies in North America,<sup>12</sup> while the MRC have used shorter five day intensification at five and 20 weeks.<sup>13</sup> Recently, randomised trials both in Europe and North America, have confirmed the benefit of additional intensive treatment at nine to 10 months from diagnosis.<sup>14,15</sup> There are many continuing trials designed to try and optimise intensification treatment.

#### CNS DIRECTED THERAPY

Treatment to prevent overt leukaemic infiltration of the central nervous system is essential for all children with lymphoblastic leukaemia, and in many past protocols this comprised a combination of cranial irradiation and a course of about six intrathecal methotrexate injections. Concerns about potential late effects of treatment, in particular, growth problems and the risk of secondary CNS tumours<sup>16</sup> prompted a reappraisal of the role of cranial irradiation in childhood ALL. Effective prevention of CNS relapse can be achieved in most children by a course of intrathecal methotrexate injections during the first three months of treatment, and continuing regular injections thereafter.<sup>17,18</sup> It is unclear whether further modifications such as combination intrathecal therapy with hydrocortisone, cytarabine, and methotrexate<sup>19</sup> or the addition of high dose intravenous dose methotrexate<sup>20</sup> improve CNS protection or event free survival.

Systemic treatment, most notably oral steroid therapy, influences the chance of CNS relapse. There is evidence from one early study that oral dexamethasone affords better CNS protection than prednisolone,<sup>21</sup> and trials in Europe and North America are investigating this. Is cranial irradiation essential for any children with ALL, except the 1–2% who have overt CNS infiltration at presentation? There are no randomised trials addressing this issue but it is possible that children with a high leucocyte count at presentation and a poor early response to treatment and/or T cell leukaemia<sup>22,23</sup> may benefit from irradiation.

#### CONTINUING (MAINTENANCE) THERAPY

All protocols for ALL still include continuing (maintenance) treatment for a period of two to

three years. Lymphoblastic leukaemia is the only paediatric cancer where this long term, low dose treatment is of benefit and the mechanism of action is unknown. Continuing treatment usually consists of daily mercaptopurine and weekly methotrexate, with periodic steroids and vincristine.<sup>24</sup> There is no evidence that, after the first 10–12 months of chemotherapy, more complicated protocols are more effective than this simple schedule. Most attempts to shorten this phase of treatment beyond two years have been associated with an increase in relapse rate.<sup>9</sup>

There has been a resurgence of interest in continuing treatment in the last few years in the hope of further reducing the relapse rate. Non-compliance may occur with this as with other oral treatments, and should be suspected in children who maintain a high leucocyte count despite maximal prescribed drug doses.<sup>25</sup> This can be confirmed by measurement of thiopurine metabolites. Patients who achieve high concentrations of metabolites during treatment have a lower relapse risk.<sup>26</sup> Similarly patients who become neutropenic during treatment have a lower relapse risk than those who consistently maintain higher leucocyte counts.<sup>27</sup> Boys tolerate higher doses of mercaptopurine than girls, and this may in some way be related to their higher risk of relapse.<sup>28, 29</sup>

These observations all support the need for close supervision and adjustment of the dose of thiopurines and methotrexate during continuing treatment. There is some evidence, unconfirmed by randomised trials, that giving the drugs in the evening<sup>30</sup> is more effective than in the morning. It has also been suggested that thioguanine may be a more effective drug than mercaptopurine,<sup>31</sup> and this issue is being investigated by the MRC in ALL97 and in North America.

#### RISK ASSESSMENT AND CHOICE OF TREATMENT IN ALL

The assessment of prognostic factors—that is, clinical and laboratory features at presentation which influence the chance of sustained remission—has become very complicated but, as table 2 illustrates, patients with ALL can be broadly categorised into three groups. The approach to treatment discussed above is appropriate for the majority of children with ALL—the standard risk group. There is still room for improvement in this group of patients and further modifications undergoing trial may achieve this. Patients in the higher risk group include all adolescents and younger children

Table 2 Prognostic factors in acute lymphoblastic leukaemia

Category	Proportion	Features
Standard risk	65%	Aged 1–9 years inclusive Leucocyte count $<50 \times 10^9/l$ No adverse cytogenetics
Higher risk	25%	Aged $>10$ years Leucocyte count $>50 \times 10^9/l$
Highest risk	8–9%	Infants under one year Hypodiploidy, Ph <sup>1</sup> chromosome Poor response to induction
Special	1–2%	B-ALL

with higher leucocyte counts at presentation.<sup>32</sup> Further intensification of conventional chemotherapy during the first six to ten months from diagnosis has decreased the relapse risk for adolescents with ALL<sup>33, 34</sup> and for other higher risk patients.<sup>35, 36</sup>

The group of patients at highest risk is a heterogeneous one. A few of these (1–2%) with B-ALL are now highly curable with short term intensive chemotherapy of the type used for non-Hodgkin's lymphoma.<sup>37</sup> Infants with characteristic cytogenetic findings and clinical features have a poor prognosis<sup>38</sup> and are now being treated on an international collaborative protocol. For some other special risk patients, for example, those with a Philadelphia chromosome, or slow response to induction treatment, high dose therapy and BMT may afford the best treatment.

#### Acute myeloid leukaemia

Patients with AML require intensive, hospital based chemotherapy which produces intense bone marrow suppression and makes great demands on nursing care. An important trial from North America involved randomisation between intensively timed and more leisurely induction therapy. The event free survival in children treated intensively was 42% at three years in comparison with 27% for those receiving standard timing.<sup>39</sup> All patients in the MRC AML10 trial (1988–95) received four courses of very intensive chemotherapy. Children with a histocompatible sibling donor were eligible to receive a BMT and the remainder were randomised to receive a fifth course of high dose therapy with autologous bone marrow rescue or to stop treatment. The results of this trial showed a considerable improvement in outcome in comparison with previous UK protocols, with an event free survival of 48% at seven years.<sup>40</sup> There was no clear benefit for autologous BMT and this finding has been confirmed in several large trials from Europe and North America which compared autologous BMT with further chemotherapy.<sup>41, 42</sup> Children in the present national MRC trial (AML12) are randomised to receive either four or five courses of chemotherapy.

Now that the outlook in AML has improved, it is possible to identify patients with a more favourable prognosis. These include children with Down's syndrome and AML<sup>43</sup> and those with leukaemia in association with certain cytogenetic abnormalities (see table 1).

#### Role of bone marrow transplants in acute leukaemia

During the past few years there have been significant advances in the techniques and the safety of bone marrow transplantation. Autologous transplantation, now largely supplanted by peripheral blood stem cells collected by leucapheresis, was developed as a means of delivering high dose treatment to patients who lacked a histocompatible sibling donor. It is safer than other forms of transplant but associated with a higher risk of relapse. There is no clear evidence that autologous BMT is of benefit in paediatric acute leukaemia.

Only about one in three children in the UK has a histocompatible sibling but the chance of finding a donor for BMT has increased because of more ready availability of volunteer unrelated donors and the expansion of the programme for storing cord blood. However there is still a lack of potential donors for families from ethnic minorities. BMT from unrelated donors is in general associated with a higher mortality than that from histocompatible siblings, but single large centres have reported equivalent survival.<sup>44 45</sup>

There are few large studies of BMT for highest risk children in first remission of ALL, but updated experience from the UK<sup>46</sup> suggests that the reduction in relapse rate is outweighed or equalled by the increased mortality. BMT in first remission of ALL should probably at present be confined to groups of patients with clearly defined very poor prognosis such as those with Ph' positive ALL or those failing to achieve remission after induction treatment.

BMT from a histocompatible sibling donor was regarded as the "gold standard" treatment for children with AML, but this view must be reassessed in the light of improvements in chemotherapy. Collaborative groups in North America continue to offer these patients BMT<sup>47</sup> but in Scandinavia and Germany most patients receive chemotherapy.<sup>43 48</sup> In MRC AML12, patients with Down's syndrome or favourable cytogenetics (see table 1) are not offered BMT in first remission.

### Relapsed leukaemia

Despite improvements in treatment, perhaps 30% of children with ALL and 45% of those with AML still relapse; management of these patients (about 130 per annum in the UK) poses a sizeable problem in paediatric oncology. Most of the relapses, at least in ALL, occur in so called standard risk patients.<sup>49</sup>

Most children with ALL, and those with AML who relapse after the first few months from diagnosis,<sup>50</sup> can achieve a second remission. The chance of prolonged second remission depends in both types of leukaemia on the length of the first remission and the type of relapse. Patients with ALL and bone marrow relapse occurring within two years from diagnosis have a very poor chance of cure whatever the second treatment. Some of those relapsing later may have prolonged remissions with chemotherapy but overall, except for children with extramedullary relapse, BMT is associated with a lower relapse rate.<sup>51</sup> There is little information about the best treatment for relapsed AML, but BMT also needs systematic evaluation in this context.

### Conclusions

There have been significant improvements in the outlook for children with acute leukaemia but these advances are only available to a minority of the world's children. The challenge is to develop affordable treatment for the vast majority who lack access to modern therapy. There is still room for improvements in conventional chemotherapy and these need evaluation in randomised trials. The role of

bone marrow transplants in first remission is evolving as chemotherapy becomes more effective. New treatments are needed for relapsed patients. Molecular diagnosis has refined the assessment of prognosis but the extra value afforded by measurement of minimal residual disease is not clear. International collaboration is needed to evaluate treatment for rare subtypes of leukaemia. Long term survivors of acute leukaemia need appropriate and sensitive follow up, discussion of which is outside the scope of this review.

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