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Review

Risk Analysis in Acute Lymphoblastic Leukaemia: Problems and Pitfalls

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INTRODUCTION

MANY YEARS have now passed since the first attempts to define prognostic factors in lymphoblastic leukaemia [1]. Even in that era, when pitifully few children were cured, it was possible to identify clinical and laboratory factors at diagnosis—age at diagnosis and the leukaemic cell mass, most readily measured by the height of the pretreatment leucocyte count—which influenced the chance of long-term remission. In succeeding years, treatment has become more successful, understanding of the biology of leukaemia has improved, and almost as many papers have been written about prognostic factors as about primary treatment. Many national and international collaborative paediatric oncology groups are running excellent randomised trials of therapy, but international comparisons of the results of treatment are hampered by the fact that each team has its own set of rules for allocation of protocols and because the rules vary in sophistication. This review examines the clinical and laboratory prognostic factors used by various collaborative groups, an exercise which demonstrates the compelling need for consistent reporting of overall results and for agreement upon which risk factors should be measured and reported.

"RISK GROUPS": A NOTE OF CAUTION

The purpose of examining prognostic factors in childhood leukaemia is to determine which patients are likely to respond well to treatment and which are likely to fail, with a view to intensifying treatment in those patients at highest risk of failure and, perhaps, reducing treatment in the others. While it is not appropriate to expose children with a good chance of cure to potentially very dangerous treatment, there are also dangers in a minimalist approach to therapy. This was illustrated in a small randomised trial, conducted by the German Berlin Frankfurt Munster (BFM) group, in which omission of late intensification in so-called good risk patients led to an increased risk of late relapse [2]. Similarly in Medical Research Council (MRC) UKALL X trials, intensification of therapy proved most beneficial to the group of children at lowest risk of treatment failure [3]. Conversely, patients at highest risk of treatment failure after conventional chemotherapy may also be at high risk of failure after intensified therapy including bone marrow transplantation. These provisos should be borne in mind in any attempts at risk analysis.

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THE PATIENT

In the 30 years since prognostic factors were first identified in acute lymphoblastic leukaemia (ALL), age has remained one of the strongest independent determinants of prognosis [4]. This is most obvious when both children and adults are treated on the same protocols. Figure 1, using data from the MRC UKALL X trials for both children and adults, shows clearly how, once infants under 1 year are excluded from analysis, the prognosis becomes steadily worse with increasing age. The reasons for this include: the biological features of ALL in each age group, for example, the increasing prevalence of Ph^1 positive ALL with increasing years, but age *per se* also appears to be important. At the other end of the spectrum, there have been many recent publications about the unique features of ALL in infancy. The poor prognosis of this group of patients is associated with a number of unfavourable clinical features, including a high leucocyte count, a predilection to CNS disease, the early B-cell phenotype, association with 11q23 chromosomal abnormalities and alterations in the *MLL* gene [5]. Thus, most collaborative groups now agree that age is a factor which should influence treatment and many have special protocols for infant ALL. Once infants are excluded, as the figure shows, prognosis worsens progressively with increasing age, children over 10 years faring worse than those aged 1–9 years [6]. The treatment of adolescents with ALL falls uneasily between paediatric and adult practice, with some paediatric groups treating patients up to the age of 20 years. It is, thus, quite difficult to assess the impact of various therapies in this age group, but there is some evidence for an improved outlook in adolescents treated by the American Children's Cancer Group (CCG) and St Jude Children's Research Hospital (SJCRH) [7, 8].

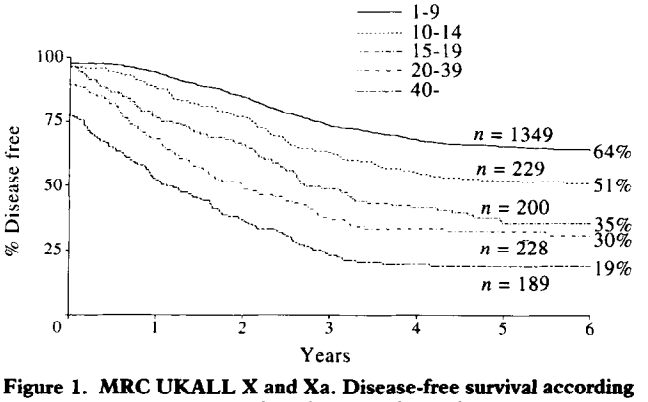

Figure 1. MRC UKALL X and Xa. Disease-free survival according to age (see key above) at diagnosis.

Boys consistently do worse than girls with ALL, but this fact may be masked by their assignment to different protocols. We have recently reviewed the outcome for boys and girls treated on MRC protocols over the last 20 years, and confirmed that, despite improvement in outcome for both sexes, boys remain at higher risk of treatment failure than girls, not just because of the problem of testicular relapse, but also because they have a higher rate of bone marrow relapse. This finding cannot be attributed to the higher prevalence of T-ALL in boys [9]. Many published results of trials have similar findings [6, 10–12] but this gender difference is seldom emphasised. The original hypothesis—that the testis acted as a sanctuary site for subsequent relapse—was not supported by trials of prophylactic testicular irradiation, which abolished testicular relapses, but did not decrease marrow relapses in irradiated boys [13]. Boys tolerate larger doses of mercaptopurine and become neutropenic on treatment less readily than girls and it has been suggested that differences in the metabolism of mercaptopurine between the sexes may play a role in influencing the success of treatment [14]. There is less clear evidence that prognosis is influenced by race, and racial differences may reflect biological variables in the leukaemia.

THE DISEASE

The classification of lymphoblastic leukaemia has progressed from the merely morphological, exemplified by the French–American–British (FAB) scheme, which is now less fashionable in prognostic assessment [15], to schemes incorporating immunophenotyping, cytogenetics and molecular biology. Moreover, the extent to which classification dictates treatment varies widely. However, there is uniform agreement that children with B-ALL, characterised by L3 morphology in the French–American–British classification, the presence of surface membrane immunoglobulin, and translocations involving chromosomes 8 and 14, 2 or 22, should receive alternative treatment with short-term high-dose protocols of the type used in paediatric non-Hodgkin's lymphoma (NHL). This approach has revolutionised their prognosis [16–18].

After exclusion of this 1–2% of cases of mature B-ALL, and the 12% or so cases of T cell origin, the other childhood lymphoblastic leukaemias are of early B-cell origin. Here nomenclature becomes increasingly confusing. Before the advent of monoclonal antibodies the epithet "common-ALL" was attached to those cases, most frequently occurring in childhood, which expressed CD19 and CD10 (CD10 being the monoclonal equivalent of the common-ALL antigen). Most collaborative groups use these two antibodies for classification, together with CD2 or CD7 to define T cell leukaemias, but the level of sophistication with which the B-cell precursors are dissected out varies widely. The American Paediatric Oncology Group (POG) have claimed that the subset of patients with cytoplasmic immunoglobulin positive leukaemia (confusingly called pre-B-ALL) had a worse prognosis than other subtypes, a claim that has not subsequently been confirmed [19]. It is now apparent that approximately 7% of children have simultaneous expression of lymphoid markers and at least one myeloid-lineage associated antigen, but this finding is of no apparent prognostic significance [20].

Do patients with T-ALL have a worse prognosis than those with B-precursor ALL, and is there a relationship between the maturational stage of T-ALL and prognosis? The German BFM group have claimed that a more immature T-cell phenotype is associated with a worse prognosis, but few other studies have analysed the subset of children with T-ALL in such detail. Our own analyses of patients treated on MRC trials shows that T-ALL is not of independent prognostic significance [9], although other groups have claimed the contrary [21, 22]. The only satisfactory randomised trial of phenotype specific therapy was performed in paediatric NHL, where it was shown that patients with B-lymphoblastic disease, analogous to the rare B-ALL, responded to short-term treatment of classical lymphoma type, incorporating cyclophosphamide and moderate dose methotrexate, whereas those with T-lymphoblastic disease had a better prognosis when treatment was given with a longer-term continuing protocol as used in ALL [23]. This question has never been formally asked in ALL, and yet some collaborative groups, such as the POG group and the CCG, have devised specific protocols either for children with T-ALL [21] or those with the so-called leukaemia–lymphoma syndrome [22], a subset of patients identified by a constellation of symptoms including organomegaly and E-rosette positivity.

The advent of cytogenetics complicated the issue even further. Groups such as SJCRH, with access to excellent cytogenetics on site, have used both leukaemia cell ploidy and the presence of specific cytogenetic abnormalities as a marker of prognosis and for risk assignment. It is more difficult to incorporate such studies into multicentre trials, but this has been successfully achieved in some studies, such as those of the POG where ploidy is deemed a strong determinant of prognosis, and publications from the group have focused on a subset of patients with hyperdiploid ALL or a high DNA index, who are highly curable with antimetabolite-based therapy [24]. Conversely the 1–2% of patients with near-haploid ALL have a high risk of treatment failure [25]. A large number of non-random chromosome changes have now been described in ALL. There is universal agreement that children with Ph1-positive leukaemia, and infants with 11q23 ALL have poor prognosis, but the previously poor outcome associated with other translocations, such as t1;19, may be overcome by more effective therapy. Molecular analysis may extend the sensitivity of cytogenetic detection in some cases, most notably infant leukaemia, where abnormalities may be identified in cases without an obvious abnormality on cytogenetic testing [26].

Cytogenetics is labour-intensive and unlikely to be universally available. In addition, there is evidence that, once patients with specific abnormalities with a well established prognosis are removed from analysis, the presence of a translocation or other abnormality is of no independent significance [27]. Thus, a common basic level of screening might be a combination of ploidy analysis with the use of probes for the few specific abnormalities with an unequivocally poor prognosis such as Ph1- and t4;11.

There is a potential discrepancy in comparisons of risk assessment in ALL between, on the one hand, large and generously endowed centres with facilities for full cytogenetic and immunological analysis and, on the other, participants in multicentre trials. These either have the option of centralised investigations, something that is difficult to ensure for all patients, or performing the tests locally with variable quality control.

TREATMENT RESPONSE

Response to treatment in individual patients has been assessed by various means including *in vitro* drug sensitivity testing [28], a day 7 or a day 14 bone marrow [29] and a short trial of steroid therapy at the beginning of treatment [11]. It is possible to

Table 1. A comparison of criteria used to assign risk groups in childhood lymphoblastic leukaemia

Study group	Year of studies	Criteria for risk assignment	Types of protocol	Percentage of children treated	References
Children's Cancer Group (CCG) 100 series	1983–1989	Age Gender Adenopathy Splenomegaly Leucocyte count Platelet count Haemoglobin level FAB morphology E-rosettes	Infants Lower risk Average risk High risk Lymphoma syndrome	2.5 24 43.5 17 13	[6] [22]
MRC UKALL X	1985–1990	Leucocyte count	All the same protocol; worst risk patients not randomised	100	[3]
Paediatric Oncology Group (POG)	1986–1991	Age Leucocyte count Immunophenotype	Infants T-ALL Various B-precursor ALL	4 80 15	[21]
St Jude Children's Research Hospital Total XI	1984–1988	Age Race Leucocyte count DNA index Cytogenetics	Lower risk Higher risk	31 69	[33]
BFM Group BFM 86	1986–1990	Blast count Mass disease Mediastinal mass Response to steroids	Standard risk group Risk group Experimental group	28.6 61.1 10.3	[11]
Dana-Farber Institute Consortium DFCI 85-01	1985–1991	Age Leucocyte count Phenotype	Standard risk Higher risk	39 61	[34]

identify 10% or so of children at higher risk of treatment failure by all these methods.

The most important factor influencing outcome is, of course, the treatment, and any set of prognostic factors may be applicable only to a particular protocol. For example, it was only with the advent of modern combination chemotherapy that it became apparent that boys had a worse outcome than girls [30]. More recently, the introduction of more intensive chemotherapy has overridden some of the adverse prognostic effects of ploidy or certain cytogenetic abnormalities [31, 32].

HOW MANY FIRST LINE PROTOCOLS?

There is a real danger that, by assigning children to a number of treatments, the overall picture may be obscured, and patients may be shifted from one risk group to another without influencing the overall outcome. It is extremely important that where many front line protocols are used, survival figures for the whole cohort of patients, as well as the subgroups are published. This becomes particularly important as treatment improves, since very large numbers of patients will be needed to demonstrate further small improvements in outcome. It is essential to compare like with like.

The present anarchic state of affairs is best illustrated by examination of recent reports of therapeutic trials. It is extremely difficult for a casual reader of the literature to compare the results of ALL treatment between various groups because of the many different methods of risk assignment and the variable number of first line protocols. The information shown in Table 1 is culled from the literature and, although by no means comprehensive, shows the many ways in which patients are stratified, and how, in publication of data on subsets of patients, it may not be possible to obtain an overall picture of the group's treatment results. The treatment approach, as shown in Table 1, has varied from that of the CCG, who have five concurrent protocols, to the MRC who traditionally adopt a more unified approach. In UKALL X, for instance, all children with ALL were eligible for entry, and only the "worst risk" 10% of patients were exempted from randomisation. The criteria used for risk assignment in these trials vary widely from the traditional age and leucocyte count, to a formula for leukaemic cell mass, response to steroids and cytogenetic analysis.

THE WAY FORWARD

The Italians, to their credit, were among the first to recognise this problem and were instrumental in hosting a meeting which devised the Rome Criteria [35] (Table 2), subsequently suggested as a standard method for reporting all trials in children with ALL. The authors recommended that, to ensure compatibility of results, all published results in childhood ALL should use (the two well established factors of) age and leucocyte count and report the proportion of patients in the categories shown in Table 2. Sadly, this suggestion has never been adopted.

If further progress is to be made in the treatment of ALL, it can no longer be possible for collaborative groups, however large, to go it alone. It will be increasingly important to compare data, and to pool results of treatment by meta-analysis. This approach will only be really possible if there is agreement to report results using a common language. A recent workshop in

Table 2. The Rome criteria for assessment of prognostic factors in childhood acute lymphoblastic leukaemia

	Initial leucocyte count before treatment	
Age at diagnosis	Less than 50 × 10⁹/l	More than 50 × 10⁹/l
Less than 1 year	Higher risk	Higher risk
1–9 years	Standard risk	Higher risk
Over 10 years	Higher risk	Higher risk

North America was held to try and agree a national uniform approach to risk classification. There was agreement to adopt the Rome criteria for age and leucocyte count. The participants also agreed to collect and pool prospective information about DNA index, early response to therapy, basic immunophenotype and "high-risk" chromosome translocations [36]. Further progress in the management of ALL depends on international collaboration. We must all, therefore, hope that this impetus will be maintained for the benefit of all patients and will be adopted outside the U.S.A.

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