Lymphoblastic leukaemia and non-Hodgkin's lymphoma

J S Lilleyman* and C R Pinkerton†

*Department of Paediatric Oncology, St Bartholomew's Hospital, London, UK;
†Institute of Cancer Research/Royal Marsden NHS Trust, Sutton, Surrey, UK

The outcome in childhood leukaemia has shown steady improvement over the last decade and efforts are now concentrated on the stratification of patients by risk factors which may avoid overtreatment of good risk patients and limit dose escalation strategies, including those with bone marrow transplantation, to the higher risk patients. In ALL, risk stratification is based on the presenting white cell count, sex, age and cytogenetics of the tumour cells. Even in acute myeloid leukaemia, the outcome with chemotherapy alone is now sufficient to limit elective allogeneic bone marrow transplantation to those who do not have cytogenetically favourable disease.

In non-Hodgkin's lymphoma, a dramatic improvement in overall survival from 50% to in excess of 80% has been achieved by an escalation in dose and dose intensity of chemotherapy. With this improvement, the prognostic influence of clinical staging has become less clear and recent efforts have concentrated on determining which groups of patients would be cured by less intensive treatment. As for ALL, there is concern about the potential late sequelae in these highly curable children. There remain groups of unusual tumour types, such as anaplastic large cell and peripheral T cell lymphoma, where there remains much to be learned about the pathogenesis and clinical behaviour. The optimum treatment strategy for these subgroups remains to be clarified.

Correspondence to:
Prof. J S Lilleyman,
Department of Paediatric Oncology,
St Bartholomew's Hospital, 4th Floor,
38 Little Britain,
West Smithfield, London,
EC1A 7BE, UK

Childhood lymphoblastic leukaemia (the prefix 'acute' is superfluous but persists in the universal acronym ALL) is an as yet incompletely understood collection of biologically distinct disorders. These do not arise with equal frequency in all ages and populations, and the point has now been reached where not all are treated the same.
Epidemiology

Despite much effort by epidemiologists over the years, relatively little progress has been made in identifying environmental or genetic factors associated with the tendency to develop ALL. This may in part be due to the fact that the majority of epidemiological studies have lumped all types of ALL together. Great attention has been focused on the potential role of ionizing radiation, either due to antenatal diagnostic X-rays, paternal occupational exposure, or direct environmental pollution, but none of these sources has clearly been shown to be causally associated with any type of the disease. There is similar concern over exposure to electromagnetic fields generated by overhead power lines, but again no study has convincingly shown there to be a link.

Arguably, the most plausible epidemiological hypothesis is that based on the idea that migration of families to new communities may be involved. It is postulated that the novel mix of infectious agents met by families moving to create new towns or communities causes some immune dysregulation in susceptible children, and that this, rather than radiation, might explain the excess of cases seen in remote nuclear power installations.

Whatever the underlying cause or causes, the incidence of ALL is not the same throughout the world. The frequency varies from 0.9–4.7 per 100,000 children per year. It is highest in Costa Rica and lowest in Kuwait and Bombay. In most countries there is a slight excess of males with a ratio of around 1.2:1. This is true for the disease overall, but is not for infants where there is a female preponderance, and is not for T-cell ALL (see below) where the male excess is more pronounced with a ratio of 4:1 (reviewed by Robison and Ross).

The incidence also varies with age. There is a well defined peak between the ages of 2–6 years, where, in the US, the rate rises to around 7 per 100,000 white children. Oddly this peak is less well defined in American black children, is not evident in developing countries and was not apparent in either the US or Great Britain until the 1930s. This has led to theories that some exposure to modern domestic developments may be involved, but incompleteness of case ascertainment 60 years ago (or even now in underprivileged communities) could be a confounding factor.

The 2–6 year peak is more exaggerated if only ‘common’ ALL is considered (see below), and is not evident if this variety is excluded and only other ALL types are considered. This underlines the importance of taking the heterogeneity of the disorder into account in epidemiological studies.

Classification

Morphology: Traditionally, ALL has been defined morphologically by the French American British group who suggested the three categories of
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L1, L2 and L3 based on microscopic blast cell appearances. This has proved clinically to be of limited value as the proportions falling into the three categories are grossly uneven and divide patients into roughly 90%, 9% and 1% respectively. There is some evidence that L2 ALL is more refractory, occurs with equal frequency in all ages (i.e. shows no 2–6 year peak), and may have a different immunophenotypic pattern. The rare L3 ALL does not respond to conventional ALL treatment. It shows a mature B-cell phenotype and frequently presents as a lymphoma. It is considered further in part 2 of this chapter.

**Immunophenotyping:** Since the first recognition of features of B and T-cell lineage and the definition of the ‘common’ ALL antigen (now CD10), ALL has been most usefully classified on the basis of immunophenotyping. Considerable progress has been made in the last 10–15 years in refining reagents and defining blast cell features. The latter are referred to as clusters of differentiation (CD) with an appropriate suffix number depending on the feature concerned. Some CDs relate to lymphocyte sublineage (CDs 1–8 mark various stages of T-cell ontogeny, CDs 19–22 and 24 mark B-cells), whereas others, such as CD10 and CD34, mark more primitive features. Other useful immunologically defined cell characteristics not given CD numbers include cytoplasmic and surface immunoglobulins (found in pre-B and mature B-ALL, respectively), terminal deoxynucleotidyl transferase (TdT, found in immature lymphoid cells) and HLA-DR, a relatively non-specific expression of class II histocompatibility antigens.

Using these tools, it is possible to classify ALL into the major categories of ‘common’ (around 50%), ‘pre-B’ (around 25%), ‘T’ (around 15%), ‘null’ ALL (around 9%) and ‘B’ (around 1%). All forms other than T-ALL are considered to be derived from some stage of B-precursor cell, and ‘null’ ALL is sometimes referred to as ‘early B-precursor ALL’. The immunophenotypic classification of ALL has recently been reviewed by Ludwig et al.

Cytogenetics and molecular genetics: Non-random changes in the chromosomes of lymphoblasts have been observed for some years, and simple studies of blast cell ploidy have also helped to categorize them (see prognostic factors, below).

Some regularly seen translocations produce fusion genes where a proto-oncogene moves into the vicinity of promoter or enhancer sequences on another chromosome. One of the most common (5–6% of all cases) is t(1;19)(q23;p13.3) seen in pre-B ALL where the E2A gene fuses with PBX1. Another is the t(9;22)(q34;q11), forming the Philadelphia chromosome and the BCR–ABL fusion gene. It arises in
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2–5% of all ALLs, and is associated with extreme resistance to therapy. Much interest currently centres around rearrangements involving the MLL gene on chromosome 11 in the q23 region. Some 70% of infants with ALL may demonstrate this, and the commonest result is a fusion gene with AF4 on chromosome 4, band q21. The poor outcome of treatment in infants with ALL is largely confined to those with some 11q23 abnormality. Recently a rare translocation, t(12;21), cytogenetically detectable in less than 0.1% of children, was cloned and shown to be part of the TEL gene fused to the AML-1 gene. Once cloned, subsequent fluorescence in-situ hybridisation studies have shown that conventional cytogenetics cannot detect this abnormality in the majority of cases, and it has proved to be the commonest single genetic lesion so far seen in childhood ALL being present in between 16 and 20% of patients. Unlike other translocations, it is predictive of a more favourable response to therapy.

Treatment

The story of the evolution of therapy for ALL is remarkable as the present position where some 60% of children can be permanently cured has been reached starting from a 100% mortality in just 40 years. Considering the different disease subtypes, though, the proportion that can be cured varies considerably (see prognostic factors, below).

‘Standard’ treatment for ALL is pretty much the same all over the world, and has evolved from the ‘total therapy’ pioneered at St Jude Hospital in Memphis in the early 1960s. It falls into distinct parts that can be considered separately; remission induction, remission consolidation, CNS directed treatment, and continuing or ‘maintenance’ therapy.

Remission induction: The main drugs used are vincristine and corticosteroids. Without other agents these two will gain a remission in over 80% of children. Adding asparaginase increases that figure to over 90%. Whether it is beneficial to add other drugs in the first few days of treatment, such as anthracyclines, is still an open question. Such agents are unlikely to improve the number of children going into remission, but could accelerate disease clearance and may provide some benefit in terms of event free survival.

Consolidation: Sometimes referred to as ‘early intensification’ or simply regarded as a second part of remission induction, it is currently common practice to give some form of multidrug combination in the first few days or weeks following the achievement of marrow clearance and the
restoration of normal marrow function. Drugs used include cytarabine, anthracyclines, etoposide, thioguanine, cyclophosphamide, vincristine and steroids. Schedules vary. Some groups use a short sharp pulse over 5 days\textsuperscript{13}, others a more drawn out programme over 8–14 weeks\textsuperscript{14}.

That consolidation therapy is valuable in the early weeks or months of treatment is no longer in doubt. The German BFM group showed this in their early unrandomized studies and the point was subsequently convincingly confirmed in randomized trials both in the US\textsuperscript{15} and the UK\textsuperscript{13}. On the other hand, the value of further ‘late’ consolidation, over 6 months after entering remission, is not so clear and is still being evaluated.

The potential long term carcinogenicity of alkylating agents, anthracyclines and podophyllotoxins commonly used in consolidation has worried some groups, and it may be possible to give effective intensification treatment based on less risky antimetabolites alone\textsuperscript{16}. So far this is not widespread practice.

**CNS directed therapy:** Cranial radiotherapy was originally the standard approach to the prevention of CNS relapse in ALL. Now it is now reserved for children perceived to be at especially high risk of CNS involvement (those with high diagnostic white cell counts or bulky extramedullary disease), or those few who have CNS infiltration at diagnosis. It is generally accepted that for others adequate protection can be achieved by intrathecal therapy either alone or in conjunction with high doses of systemic methotrexate with folinic acid rescue, though it appears to be important to continue intermittent intrathecal injections for a full 2 years if no radiotherapy is given\textsuperscript{17}. Whether intrathecal methotrexate on its own is sufficient or whether adding cytarabine and hydrocortisone is beneficial is unclear\textsuperscript{18}.

The avoidance of cranial irradiation is motivated by the growing appreciation of the intellectual and endocrinological damage it can cause, particularly if given to very young children (see problems for long survivors, below). In the UK, children under 2 years are never given radiotherapy, whatever their perceived CNS risk.

**Continuing ‘maintenance’ treatment:** One of the mysteries of ALL therapy is why this phase of treatment is effective or necessary. That it is important is undoubted\textsuperscript{19}, but ALL is unique among human cancers in the way it responds to continuous low-dose oral antimetabolites. The various regimens used are more akin to the management of autoimmune disease or immunosuppression following organ transplantation than a cytotoxic onslaught on malignant disease. But no successful protocol for ‘common’ ALL has been described where an extended period on a thiopurine and an antifolate has been excluded\textsuperscript{20}. Most also include
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'pulses' of vincristine and steroids, and a few include cycling 'blocks' of consolidation type multi-drugs. The former may be of benefit\textsuperscript{21}, but the latter confer no obvious advantage for most patients.

It is likely that different sub-types of ALL respond to 'maintenance' differently. T-ALL sufferers may benefit from the addition of cytarabine and cyclophosphamide pulses\textsuperscript{22}, and it has been appreciated for some time that the few B-ALL patients do appallingly on conventional ALL treatment but do well on aggressive short-course multidrug schedules (see lymphoma treatment, further in this chapter).

**Prognostic factors**

The outlook for children with ALL has steadily improved over the last 20 years. Treatment itself is, of course, the most important prognostic factor against which all others pale. But if an unselected cohort of children is treated similarly certain features can be identified that can be used to predict outcome. Few of these are completely independent of each other, and many relate to particular disease subtypes. The more important are listed below.

**Diagnostic white cell count:** The diagnostic white cell count has been noticed for many years to be important. The lower the better. There is no magic threshold. Children with high counts are more likely to relapse, and this remains true for up to 2 years from diagnosis. But after that, if they continue in their first remission, high count children have the same outlook as everyone else\textsuperscript{23}. White count variability is not evenly distributed between ALL subtypes. Infants with t(4;11) and children with T-ALL, for example, have higher counts than others.

**Age:** Age influences outcome, with infants and older children faring worse than those in the 2–6 year range. Again, this partly reflects the incidence of different subtypes and emphasises the good prognosis of those with 'common' ALL, low white counts and hyperdiploidy who are over represented in the 2–6 year olds. That may not be the whole story, though, as it appears that older children and adolescents have a worse outlook than younger children even if their disease type is taken into account.

**Gender:** Gender is important for prognosis. In most (but not all) studies, girls have had superior event free survival to boys\textsuperscript{24}. The phenomenon is not explained by testicular disease, nor a skewed distribution of ALL subtypes (even though T-ALL is 4 times commoner in...
boys). The disparity does not become apparent until some 2 years from diagnosis and may be partly explained by a differential failure of 'maintenance' therapy in boys. Why is not known, but they appear to tolerate higher doses of antimetabolites on similar prescribing criteria and it is possible that they may have a different pattern of intracellular enzyme activities or simply be more delinquent compliers.

Based on the UK trials VIII and X, the three factors of white count, age and gender have been used in a Cox regression analysis to derive a 'hazard score' with boundaries set to define children with a 5 year disease free survival of less than 40%. This indicates, for example, that a 6 year old boy with a diagnostic white count of \(200 \times 10^9/l\) would be classified as 'high risk' whereas a girl of the same age would not.

**Blast cell ploidy:** Blast cell ploidy is related to disease subtype and outcome. There are several ploidy groups in ALL but only two have clinical importance at present. Hyperdiploidy (>50 chromosomes) is seen in around a third of all patients, is associated with the age range 1–10 years, a low presenting white count, and the immunophenotype of 'common' ALL. It heralds a good response to conventional therapy. The converse, hypodiploidy (<45 chromosomes) is seen in 5–10% of children and predicts resistant disease.

**Abnormal fusion genes:** Some abnormal fusion genes, notably BCR-ABL or MLL-AF4, indicate highly resistant disease and children who have them fare very badly on conventional therapy.

**Speed of response:** Speed of response to treatment appears to be important, as children clearing their marrows of disease in 14 days have a superior long term disease free survival. The late persistence of residual disease detectable only by polymerase chain reaction amplification of RNA or DNA unique to the malignant clone (fusion gene transcripts or junctional regions generated by immunoglobulin or T-cell receptor gene rearrangements) also appears to be an adverse finding though subsequent relapse can be very delayed and possibly is not invariable.

**Treatment of relapse**

Relapse at any site at any stage is a serious event and subsequent long disease free survival following salvage therapy is still for a small minority. Previous therapy and the length of the first remission are important factors. Marrow relapse within 3 years of presentation is probably best treated with allogeneic progenitor cell transplantation, whereas later relapsers, particu-
larly those whose recurrence is isolated to the testis, may respond well to a second programme of (more intensive) chemotherapy alone\textsuperscript{31}. The best way to treat isolated central nervous system disease is not clear, but most who suffer it eventually have a marrow relapse, so unattenuated systemic treatment should be given as well as CNS directed measures\textsuperscript{32}.

**Problems for long survivors**

The worst problem that long survivors can encounter is a second malignancy or other life threatening late event. There is a 20-fold excess of brain tumours amongst those who have had ALL, particularly (but not exclusively) those who received cranial irradiation before the age of 5 years\textsuperscript{33,34}. Treatment schedules with considerable exposure to epipodophyllotoxins have produced an increase in secondary acute myeloid leukaemias\textsuperscript{35}, an otherwise rare event in ALL survivors, and anthracyclines have taken their toll on the heart by leading to late cardiac failure in a few unfortunate individuals\textsuperscript{36}.

Other problems are less catastrophic but not trivial. Children treated with cranial radiotherapy can have problems with growth and development due to dose dependent damage to the hypothalamic-pituitary axis. Those most at risk are patients treated with high doses (> 2400 cGy) at a younger age, and such children not infrequently suffer short stature and obesity in later life\textsuperscript{37}. Girls are also at risk of precocious puberty, leading to severe curtailment of final height especially if associated with secondary growth hormone deficiency\textsuperscript{38}. Whether chemotherapy alone can impair growth to a clinically important degree is less clear. It possibly can\textsuperscript{39}.

Testicular irradiation renders males sterile and most will need androgen replacement through puberty. Chemotherapy may lead to sub-fertility which can improve with time\textsuperscript{40}. Ovaries are less sensitive and usually function normally unless they have been irradiated.

Intellectual impairment is evident in some survivors, manifest as a fall in IQ of 10–20 points. Whether this phenomenon is radiation induced, chemotherapy mediated, age-related or progressive remains uncertain, and prospective studies are in progress comparing different modalities of CNS directed treatment. The whole field of late effects of ALL therapy has recently been reviewed by Jenney and Kissen\textsuperscript{38}.

**Non-Hodgkin’s lymphoma**

**Pathological classifications**

The classification of non-Hodgkin’s lymphoma in adults has been bedevilled by a number of different pathological classifications over the
Table 1  REAL classification. (Selected groups as registered with UKCCSG central pathology review panel.)

<table>
<thead>
<tr>
<th>B-cell neoplasms</th>
<th>%</th>
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<tr>
<td>Precursor B neoplasm</td>
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</tr>
<tr>
<td>Precursor B lymphoblastic</td>
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</tr>
<tr>
<td>Peripheral B neoplasm</td>
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<td>Diffuse large B cell</td>
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<tr>
<td>— Primary mediastinal (sclerosing)</td>
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<tr>
<td>Burkitt's</td>
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</tr>
<tr>
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<td>4</td>
</tr>
<tr>
<td>T-cell neoplasms</td>
<td></td>
</tr>
<tr>
<td>Precursor T neoplasm</td>
<td></td>
</tr>
<tr>
<td>— Precursor T lymphoblastic</td>
<td>20</td>
</tr>
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</tr>
<tr>
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</tr>
<tr>
<td>Anaplastic large cell</td>
<td>15</td>
</tr>
<tr>
<td>Non-specified/indeterminate</td>
<td>9.2</td>
</tr>
</tbody>
</table>

last 20 years. The most widely used to date is the Working Formulation which separates the patients on the basis of likely clinical behaviour into low-grade, intermediate-grade, and high-grade. The Keil classification was modified in 1988 to take into account advances in immunophenotyping. This divided tumours into two broad groups as B and T neoplasms and separating into low-grade and high-grade for each. In paediatric practice, a much simpler classification has been possible because of the fewer different histological sub-types. In the US, most studies have separated patients on the basis of standard morphology into diffuse lymphoblastic (usually T-immunophenotype), diffuse undifferentiated (usually B phenotype), and diffuse large cell, (B or T). This classification has served well until recently and enabled treatment strategies based on the two commonest morphological types to be developed. More recently, however, the situation has become complicated by the routine and increasingly sophisticated immunophenotyping of these tumours. Although over 60% still fall into the two commonest groups namely T-lymphoblastic and Burkitt's or Burkitt-like B-cell lymphoma, there is increasing confusion about the less common sub-types both with regard to terminology and treatment.

A recent attempt to update the classification of lymphoma was published in 1994. The so called REAL classification (Revised European American Lymphoma classification) is essentially an expansion of the Keil classification. It makes no attempt to divide patients on the basis of clinical outcome and this has been criticised.

Only a minority of tumours in the new REAL classification are types found in paediatric practice. In Table 1 the results of central pathology review on over 200 paediatric lymphomas registered with the United Kingdom Children's Cancer Study Group (UKCCSG) are summarised.
Kingdom’s Children’s Cancer Study Group (UKCCSG) are outlined and classified according to the REAL classification. As can be seen, 42% are Burkitt’s (B-NHL) and 20% T-lymphoblastic (T-NHL). Of note is the high percentage (15%) of anaplastic large-cell lymphoma (ALCL). This diagnosis is made increasingly frequently with the wide spread use of CD30 (K1) antibody. The remaining tumours include those which in the past would have been included under the broad heading of diffuse large cell lymphoma and a small number of precursor B lymphoblastic neoplasms equivalent to pre-B or CALLA positive leukaemia. It is to be hoped that an attempt will be made by paediatric oncologists and haematologists to utilise the REAL classification in future studies in order to standardise terminology. This is the intention in the CCG/UKCCSG/ SFOP collaborative trial for peripheral B cell neoplasms.

Clinical pathological correlates

Despite a general overall improvement in the outcome of most histological sub-types morphology is still of relevance. With most intensive multi-agent regimens, the overall cure rate for B-NHL is around 80% ranging from 60% for those with stage 4 CNS positive disease to 100% for localised stage 1 disease. This compares with around 60% for T-NHL when a leukaemia type chemotherapy regimen is used and around 60% for anaplastic large cell lymphoma when either a B or T cell based protocol is used. In the case of large cell lymphoma, B lineage has been shown to confer a favourable outcome with 96% survival at 3 years compared to 67% for T and indeterminate lineage tumours. B lineage was also associated with lower stage. In this study neither CD30 expression or anaplastic large cell morphology had any prognostic significance.

As discussed later, the distinction between peripheral T cell lymphoma (PTCL) and ALCL remains unclear, and although in adults these tumours have been said to behave in an aggressive manner this remains to be demonstrated in children. Moreover, it seems likely that most of the tumours previously in this category would now be considered as CD30 positive ALCL.

Even more uncommonly low or intermediate grade lymphomas may be found. In a review from St Jude’s, 3% fitted this category. Of those, half were follicular and the others diffuse low or intermediate grade. Outcome for both groups was excellent as might have been predicted, although treatment strategies varied widely with regard to the intensity of chemotherapy and the use of radiotherapy.
Burkitt’s lymphoma (BL) was one of the first tumours in which the nature of molecular alterations were clearly defined. 80% of BL carry a t(8;14) translocation and the others either t(2;8) or t(8;22). This results in the juxtaposition of the c-myc locus to the locus of immunoglobulin heavy chain or κ or λ light chains. The sites of breakage in chromosome 14 are distributed throughout the heavy chain locus and translocations may occur near regions which are prone to physiological rearrangement during the normal sequence of VDJ recombination or isotope switching. The c-myc gene consists of three exons and the translocation, in general, leaves the c-myc coding region intact. This suggests that the consequent behaviour is a reflection on c-myc deregulation rather than mutation in the gene. Endemic and sporadic BL have been reported to differ at a molecular level which may reflect differing aetiology. Endemic cases do not carry rearrangements of c-myc genes detectable by conventional southern blot and most of the breakpoints lie far 5′ of c-myc on chromosome 8 and on chromosome 14 involve limited D and J segments. These tumours usually have low levels of surface Ig (mainly IgM) and secrete little immunoglobulin. Sporadic Burkitt lymphomas usually have higher levels of surface Ig and Ig secretion. These tumours usually exhibit rearranged c-myc loci with the translocation immediately upstream or within the c-myc transcription unit on chromosome 8 and within switch region on chromosome region 14. It seems possible that these translocations are at a later stage of B cell differentiation when the switch recombinase enzymes are active. These molecular mechanisms are not only of interest in terms of potential pathogenesis but have also been utilised both for detection of minimal residual disease and possible novel therapeutic manoeuvres. Minimal disease may be detected by conventional cytogenetics or PCR directed at tumour specific patterns of immunoglobulin gene rearrangement.

The molecular features of B cell leukaemia are similar, if not identical, to sporadic B cell lymphoma and it seems likely that the same applies to T lymphoblastic NHL and T-ALL. Although specific translocations are relatively uncommon in T-NHL, molecular analysis reveals that ~25% of cases with T-ALL have a small deletion of TAL-1 gene on chromosome 1, which occasionally is associated with a t(1;14) translocation. It is not yet clear if these changes occur in paediatric T-NHL. The tumour specific molecular changes or patterns of T cell receptor rearrangement may be useful for detection of minimal bone marrow involvement at presentation in T-NHL in a similar fashion to that used in T-ALL. Recent interest has focused on cyclin dependent kinases CDK4 and CDK6 which are regulated by the p16/p15 genes on chromosome 9. These act as negative regulators of cell cycling. Deletions of either one or both of these genes

Molecular biology and genetics
occurs in a small percentage of cases of T-ALL and may occur in T-NHL.\textsuperscript{51,52}

The anaplastic large cell lymphoma subgroup is becoming increasingly important and its molecular characteristics are now being more clearly defined. The presence of a t(2;5) translocation has been known for several years.\textsuperscript{53} It is intriguing that this translocation has also been reported in Hodgkin’s disease and it seems possible that a group of ALCL may be part of a Hodgkin’s spectrum.\textsuperscript{54} The relationship between the translocation and outcome is also of interest and a recent study has suggested that there is a subgroup of tumours in which either the t(2;5) translocation or other abnormalities of 2p are found where the disease tends to be more advanced, B symptoms more frequent, hepatosplenomegaly common and the outcome very poor.\textsuperscript{55}

**Clinical prognostic factors**

The Murphy staging system for NHL is shown in Table 2. This has remained broadly applicable to T-NHL despite the improvement in the effectiveness of chemotherapy over recent years. There is little difference in outcome between stage I and II patients although, as discussed later, the treatment for this group remains somewhat controversial. For non-localised stage III and IV, T-NHL relapse free survival is in the region of 70% and 60%, respectively. It has recently been suggested that the resolution of radiographic abnormalities in the mediastinum maybe a useful prognostic factor.\textsuperscript{56} The survival in the 25% of patients in whom there was incomplete resolution of chest X-ray abnormalities by day 60
following the start of treatment was significantly worse than those in whom X-ray had returned to normal (84% vs 56% 5 year survival). More intensive local and systemic therapy may be required for the latter group.

In the case of B-NHL, the cure rates for stage I and II now approach 100% with appropriate chemotherapy and the difference between stage III and IV has become less clear with relapse free survival approaching 90% for both. With the less intensive, less effective chemotherapy regimens used in the past, clinical features could separate prognostic groups within stage III. For example, patients with nodal abdominal disease did significantly better than those with extra abdominal sites and other organ involvement. The presence of a plural effusion was also noted to be a bad prognostic factor. LDH has been a persistently useful prognostic indicator and even with the current regimens appears to predict a small (~10%) difference in outcome. In some regimens, treatment is stratified on the basis of initial LDH. A current collaborative Anglo French study evaluates the potential prognostic influence in stage III patients of LDH, initial tumour bulk, response to treatment, initial nutritional status, and sites of disease. LDH is emerging as the only significant factor.

Delay in attainment of complete remission is important, and intensification of chemotherapy, including megatherapy and stem cell rescue, is indicated for patients with biopsy proven residual active disease after three months chemotherapy. High dose therapy in these initial partial responders appears to significantly improve outcome.

On the basis of LMB 1984 data stage IV patients in the current SFOP/UKCCSG studies with more than 70% blasts, B-ALL disease distribution (predominantly bone marrow with peripheral nodal disease) and those with initial CNS involvement are regarded as poor risk. There appears to be little difference in outcome between these patients with up to 70% bone marrow involvement and stage III disease. Where there are more than 70% blasts/BALL or CNS positive disease, more aggressive CNS directed therapy has been introduced and the relapse free survival now approaches 70%.

For anaplastic large cell lymphoma, the Murphy classification is unsatisfactory and it is clear that a novel approach to this disease is required. The unusual distribution with skin involvement and parenchymal lung disease does not really fit into the current classification. Moreover, the rarity of bone marrow or CNS disease makes stage IV very unusual. There is an urgent need to analyse large series of patients treated in a standard fashion to clarify the prognostic impact of clinical features such as weight loss and high fever at presentation, skin and lung involvement, hepatosplenomegaly and response to treatment. Clues may come from biological factors as discussed earlier.
Chemotherapy strategies

For the past 15 years, the chemotherapy strategy for childhood NHL has been largely based on the important observations in the CCG randomised trial for non-localised NHL. This showed a significantly superior outcome for patients with lymphoblastic disease who received a leukaemia type prolonged multi-agent regimen (LSA2L2) in contrast to those with diffuse undifferentiated lymphoma where a shorter pulsed cyclophosphamide based regimen produced superior results. As a consequence, in most groups T-NHL is treated in a similar manner to T-ALL whereas those with B-NHL receive a pulsed cyclophosphamide based regimen.

Localised disease

In the past, patients with localised B or T lineage disease fared relatively well irrespective of the chemotherapy regimen given. In the UK, the practice in recent years has been to treat Murphy stage I and II T-NHL on the basis of immunophenotype and use a prolonged leukaemia type regimen identical to that used for T-ALL. For B lymphoblastic disease a short CHOP based regimen is used. Because of the high cure rate and concern about late morbidity, some groups have dropped either cyclophosphamide or doxorubicin from these regimens. Others have simply shortened the treatment to 6-8 weeks' duration. The required treatment intensity for localised T-NHL remains unclear but there are suggestions from a number of studies that, as the relapse pattern resembles T cell leukaemia, (often late and involving bone marrow) more prolonged treatment therefore may be appropriate. Moreover, it could be argued that an ALL regimen where cyclophosphamide is omitted and the anthracycline doses are minimal may carry fewer late effects than a B cell pulsed regimen, particularly in boys.

Non-localised disease

The management of Murphy stage III and IV T-NHL is less contentious and in the UK is again identical to the T-ALL regimen. In some protocols, CHOP is added to this regimen but, in the view of potential late toxicity and unproven benefit it seems inappropriate. A recent UKCCSG study (NHL9004) has electively omitted cranial radiation and substituted high dose methotrexate. This has not been associated with any significantly increased incidence in CNS disease and overall up to 70% of children will be cured. The use of
radiotherapy to localised bulk disease is of unproven value. Although a single randomised study suggested a benefit, the treatment was given with what was probably suboptimal chemotherapy. There may, however, be a place for local radiotherapy in refractory mediastinal disease.

Non localised B-NHL is now highly curable with appropriate pulsed chemotherapy. The development of regimens containing high doses of cyclophosphamide, methotrexate and cytarabine has demonstrated the dramatic impact of dose escalation of standard agents in a chemosensitive disease. The early trials from St Jude, BFM and SFOP/UKCCSG have all clearly demonstrated this effect. Inevitably, the morbidity, and in some cases the early mortality, of these regimens is unacceptably high and the new POG/UKCCSG/SFOP collaborative study will address the issue of both the dose of cyclophosphamide and the duration of chemotherapy in stage III and IV disease.

Management of uncommon sub-types

With the increasing application of detailed immunohistochemistry and molecular pathology, it is becoming more difficult to apply standard pathologic classifications to those tumours which do not fit into the categories of Burkitt or Burkitt-like B lymphoblastic lymphoma or T lymphoblastic lymphoma. For this reason, trying to base treatment strategies on retrospective published data is particularly difficult. For example, as recently a 1994 major review of ‘large cell NHL in childhood’ divided pathological sub-groups into; immunoblastic, diffuse, diffuse mixed and follicular. A review of the treatment in a series of peripheral T cell lymphomas showed that the vast majority were CD30 positive and would, therefore, now be grouped within the anaplastic large cell group. Similarly, patients previously grouped as malignant histiocytosis would almost certainly now be grouped under the ALCL definition. Review of outcome of ‘extra thoracic T-NHL’ inevitably includes a wide range histological subtypes.

Anaplastic large cell lymphoma

This is a disorder which is being diagnosed increasingly frequently and it is important that a treatment strategy is evolved for such patients. Unfortunately, the published data are very unclear as to the most appropriate management. This is compounded by the very variable clinical behaviour ranging from spontaneous resolution of skin disease to aggressive disease necessitating high dose chemotherapy with bone marrow transplantation. The variation in the presenting features is...
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striking with, in particular, involvement of lung, skin and bone. The biological features of ALCL are becoming more clearly defined although the precise prognostic impact of CD30 positivity or t(2;5) translocation remain unclear. In general, there have been two broad approaches to treatment using either chemotherapy designed for other childhood NHL of T lineage, i.e. a leukaemia type approach, or that used for B cell tumours. The largest study to date is from the BFM group who reported encouraging results using their NHL 83, 86 and 90 protocols. Overall, the probability of event free survival was 81% and by univariate analysis only the presence of splenomegaly and skin involvement had an adverse association with event free survival.

The UKCCSG has adopted a similar strategy and treated patients with Murphy stage III and IV with an intensive B cell regimen similar to the SFOP/LMB protocols. Patients with localised disease receive a shorter less intensive CHOP based regimen. Although in other series the overall outcome with less intensive treatment appears comparable, it is essential that larger numbers are treated with standard protocols. In the St Jude’s study there appeared to be a better outcome in patients with CD30 expression compared to those diagnosed on morphological grounds alone. In the past, the treatment of so called malignant histiocytosis was a CHOP type regimen. This diagnosis is now virtually never made in paediatric practice.

As discussed earlier, most peripheral T cell lymphomas in childhood would now be considered to be ALCL. In a series of 28 patients with ‘peripheral T cell lymphoma’, 22% were said to be ALCL on morphological grounds although a higher percentage were found to have a t(2;5) translocation and, moreover, 25 of 27 evaluable were CD30 positive. There is probably a small sub-group of children with non CD30 positive PTCLs where it seems unlikely that a sufficient number will be treated with single protocols to clarify what treatment is best. In children with large cell lymphoma of non T lineage, a standard B cell type treatment is likely to result in a favourable outcome.

Primary mediastinal B cell lymphoma

This unusual subgroup is commonest in adolescents and young adults and in females. Marrow and CNS are not usually involved, but clinically it may be difficult to distinguish from T lymphoblastic lymphoma. The limited information available in children and adults suggest that the appropriate treatment is an intensive CHOP based regimen similar to that used for B cell lymphoma and the current is UKCCSG strategy to treat in a similar manner to a stage III Burkitt lymphoma. It appears that
mediastinal radiation is not required provided a complete response is achieved with primary chemotherapy. CNS directed therapy is probably not required although CNS disease has been found at relapse in some cases. The majority of failures are at the mediastinal site.

Follicular lymphoma

Low or intermediate grade lymphoma are extremely rare in childhood and probably follow a similar pattern to that seen in adults. In a series of 17 cases, all but one survived following CHOP based chemotherapy with additional radiotherapy and maintenance chemotherapy in some cases. These patients must, however, be followed up for a prolonged period as late relapses can be seen.

Immunosuppression related NHL

With the increasing use of strongly immuno-suppressive agents such as cyclosporin A, anti T cell antibodies and FK506 for organ transplantation, these tumours are a more frequent clinical problem. The majority are of B cell origin and may be either ‘non-malignant’ lymphoproliferative disorders (LPD) associated with EBV infections or true lymphomas. In the former there may be resolution following reduction in the immunosuppression therapy but in some the disease progresses leading to a significant mortality. The biological features of disease which is likely to respond spontaneously or develop into aggressive tumours remain unclear. This is the subject of a national prospective registry run by the UKCCSG. It is planned to document the EBV status of both patient and tumour in addition to molecular cytogenetic characteristics and immunophenotype, and to correlate these with behaviour.

The UKCCSG treatment guidelines for such tumours are that if there is no spontaneous resolution on withdrawal of immunosuppressive drugs, then weekly courses of low dose cyclophosphamide, vincristine and prednisolone are given. Should this fail to achieve a complete response or if disease recurs shortly after cessation of COP then a standard multiagent B lymphoblastic NHL regimen is instituted. Alternative strategies for these patients have included anti B cell monoclonal antibody therapy or the adoptive transfer of viral specific T lymphocytes in the allograft.

Role of high dose therapy

The interest in high dose therapy in NHL has waned over the last 10 years with increasing evidence that moderately high dose pulsed
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chemotherapy is effective in the majority of cases without the need for stem cell rescue. There remain, however, a minority of patients where this is appropriate. These include children with B-NHL who fail to achieve a complete remission after 12–16 weeks of treatment and also following disease relapse. Even where disease recurs following intensive modern protocols, provided a second remission can be achieved, it is appropriate to consolidate this with high dose chemotherapy including a combination such as BEAM (BCNU etoposide, cytarabine and melphalan) or cyclophosphamide and total body irradiation using allogeneic or autologous peripheral stem cell rescue.

CNS disease continues to have a comparatively poor outcome although recent data from the LMB and BFM groups indicate that over 70% of these children will be cured as a consequence of dose escalation of cytarabine and methotrexate without the need for high dose therapy. In T lymphoblastic lymphoma, intensification treatment for a group of children whose tumour shows a slow response may improve outlook and there may be a role for mediastinal radiotherapy in these patients. The current UKCCSG NHL trial will explore the potential benefit of a third intensification block given at around 6 months. After relapse, high dose therapy with stem cell rescue should probably be used in a similar manner to that in T-ALL. Autografts may have a role where nodal relapse alone occurs.

**Novel treatment strategies**

Antibody therapy is under evaluation in a adult high grade NHL using anti CD21 and Campath antibodies. Antisense oligonucleotide treatment has been investigated in vitro. In a high proportion of Burkitt's lymphoma, n-myc gene transcription is aberrant with loss of the normal splice pattern. These tumour specific intragenic sequences can act as targets for oligonucleotide therapy.

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