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Editorial

Childhood Acute Lymphoblastic Leukaemia

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ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL) has provided a model for cancer research over the past 40 years, but despite greatly increased knowledge about the disease, including some remarkable advances in treatment, many questions remain unresolved. Professor John Lilleyman's Update on ALL in this issue of the Journal (pages 85–90), in which our current understanding of the disease and current clinical practice are reviewed, is therefore timely, and a valuable contribution to the literature.

Various environmental factors and predisposing genetic preconditions have been considered in the aetiology and pathogenesis of ALL. However, there is still no method for predicting which individuals will be affected. This also holds true for the response to treatment. Various features may be related to outcome, and patients can be stratified into risk groups requiring more or less intensive treatment, but we cannot predict relapse in an individual patient.

Structural chromosome changes, e.g. the Philadelphia translocation t(9;22), or t(8;14) or t(1;19), are relatively common and are often associated with a distinct immunological phenotype. For example, the translocation t(9:22) is most commonly found in c-ALL, but can also, albeit rarely, be detected in T-cell ALL. Despite its poor prognostic significance overall, approximately one third of patients with $Ph1^+$ ALL will be long-term survivors. Hyperdiploidy is a prognostically favourable subset of ALL. Nevertheless, approximately 10–20% of patients experience relapses. Thus, many biological, cytogenetic and molecular characteristics contribute to better classification of ALL, but even with the most elaborate techniques, we still do not understand why they exert their presumed effects in only a proportion of affected individuals.

Even the general view that a given genotype corresponds to a distinct phenotype is not always true: despite clearly detectable molecular biological configurations, the clinical and morphological appearance is still ALL. Although one might ask whether all of these biological features used for classification and prognostication are only epiphenomena and do not reflect the true underlying genetic defect, it appears that classification of ALL would be more appropriate if it was based on genetics rather than on immunophenotyping.

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A body of literature exists on techniques to characterise leukaemic cells and has given at least some insight into possible pathogenetic mechanisms. Much less effort has been spent on exploring the possible impact of the host environment on interaction with leukaemia or of the drugs used for treatment. Patients with hyperdiploid c-ALL and more accumulation of methotrexate polyglutamates or thiopurine metabolites in erythrocytes have a better outcome than others [1, 2], emphasising the importance of so-called "maintenance therapy". We know that this phase of treatment is essential, but its mode of action is still poorly understood [3]. *In vitro* resistance to a variety of drugs is likely to result in treatment failure [4], whereas rapid early response to therapy is, as noted by Professor Lilleyman, associated with a favourable outcome.

Although the statement that treatment is the most important factor is probably correct, it is obvious that specific disease characteristics, pharmacological and host factors are interrelated. Modern approaches might consider these interactions when selecting appropriate treatment for the individual patient, but most treatment concepts rely on relatively non-selective therapy, and still the "more is better" philosophy is the basis of most currently used protocols. Although successful in the past, this philosophy ought now be changed to "more *specific* is better". Tailoring therapy to the needs of the individual patients is also desirable to reduce its early and late toxicity. Studies on detection and monitoring of minimal residual disease have shown that patients with longer detectable disease have a higher probability of relapse than others. However, the mechanisms by which leukaemic cells are controlled or eliminated are still poorly understood. Is residual leukaemia eliminated by maintenance therapy or by immunological host defence mechanisms or by both?

From the experience with allogeneic stem cell transplantation, it is likely that immunological mechanisms play an important role. In contrast to high-dose therapy followed by autologous stem cell rescue, allogeneic transplant is a very potent form of immunotherapy, usually appearing clinically as graft versus host disease. To what extent are host immune mechanisms generally involved in control or elimination of leukaemia? How can the phenomenon of very late relapses be explained? Are these the consequences of inborn or acquired deficiency of a specific host defence mechanism? The much higher incidence of leukaemias in

immunodeficient individuals, "unexpected" relapses in patients lacking poor prognostic features and the occurrence of very late relapses would be compatible with this hypothesis.

In a subset of children, leukaemia cannot be eradicated by standard chemotherapy alone. In some, imminant relapse can be suspected early by biological features such as the Ph1 chromosome or insufficient response to initial treatment, but usually relapse is unexpected. For both, allogeneic stern cell transplantation is likely to be the only curative treatment [5]. Because of their dismal prognosis, the search for allogeneic grafts should now be extended to unrelated donors, and even "investigational" procedures such as haploidentical, cord blood or autologous transplants may be justified in the context of controlled co-operative clinical trials.

The statement that prognosis has steadily improved over the past years is not quite true. Important progress was made in the 1970s and early 1980s when the BFM group reported long-term event-free survival (EFS) rates of around 70% [6]. Since that time, treatment results have slightly increased by (a) lowering the treatment-related mortality with better supportive care; (b) by altering therapeutic concepts [7]; (c) by reducing the incidence of testicular relapses by the introduction of high-dose intravenous methotrexate, and (d) by the more frequent use of marrow ablative/stem cell transplantation. However, even today the EFS rate for an unselected population of ALL patients with front-line therapy will not exceed 75%. Does this not mean that currently used tools are insufficient for the remainder? If so, we are challenged to spend more effort on improving our knowledge, and, once we are successful, this may hopefully translate into designing better and more specific treatment for all patients, leading to a reduction in both morbidity and late adverse sequelae.

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