Towards Personalised Medicine in Childhood Acute Lymphoblastic Leukaemia

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Abstract
Childhood leukaemia is one of the success stories of modern medicine. Initially advances were made by using progressively more intensive multi-agent chemotherapy regimens for all children. More recently, it has been appreciated that individual children differ considerably with respect to the sensitivity of their leukaemic cells to chemotherapy and also their susceptibility to treatment-related toxicity. This has led to a move towards more personalised treatment. The mainstay of this approach is the use of minimal residual disease measurement which assesses each patient’s response to initial therapy and enables treatment modifications to be made in real time. Personalised approaches also extend to identifying children at risk of drug toxicity using pharmacogenomics and the use of molecular techniques to identify mutations in leukaemic cells that can be specifically targeted by new drugs. This article reviews the techniques and strategies in current use and speculates on how advances in interpreting the explosion of genetic information becoming available may improve treatment for children with leukaemia in the future.

The treatment of childhood acute lymphoblastic leukaemia (ALL) is a modern-day success story. From an almost universally fatal disease in the 1950s and 1960s, a child diagnosed with ALL today can expect a cure rate greater than 85% [1, 2]. The chemotherapy drugs used to tackle ALL have remained essentially unchanged for the last 30 years so what underlies this remarkable achievement? Study of progressive therapeutic trials has shown that step-wise improvement between 1960 and the 1990s has occurred largely due to better scheduling of drugs, recognition of the need to provide adequate therapy directed against disease in the central nervous system and the advent of much improved supportive care. The latter includes not only the availability of new antimicrobial and antifungal medications and formulations but also advances in our understanding of how and when to deliver these drugs, with a shift from use in confirmed infections to pre-emptive and prophylactic use.
Another reason for improved outcomes is the willingness by physicians and families to accept more toxicity from drug treatment in anticipation of a greater chance of cure. Treatment for leukaemia remains highly intensive with a small but significant risk of treatment related mortality particularly due to infective deaths. We are now at the point where the risk of death from the treatment is nearly equivalent to the risk of death from relapsed leukaemia – particularly in patients with so-called ‘low-risk’ disease. This has necessitated a paradigm shift in leukaemia treatment protocols. Previous trials generally compared the current gold-standard drug combination with a combination of drugs (usually more intensive) that might improve leukaemic cell kill. However, since the early 2000s leukaemia trials have started to address whether treatment intensity can actually be reduced for some groups of children. In this article, the ways in which this has been achieved will be reviewed as well as discussion as to how further advances might be made in ‘individualising’ treatment for leukaemia. Of course it should not be forgotten that despite this remarkable success story there are also children whose disease is extremely difficult to treat. New advances that might help these patients will be discussed.

Overview of Acute Lymphoblastic Leukaemia Therapy

In 1948, it was first reported that temporary remissions could be induced in ALL using anti-folate drugs [3]. Further active agents were soon identified, but the next real advance came when it was discovered that the use of multiple chemotherapy agents given over a prolonged period in different combinations, so-called ‘total therapy’, rather than use of single agents could produce long-term remissions and even cure in some patients [4]. Thus, ALL became the first human cancer to be cured by drug therapy alone. The total therapy regimens used in the 1950s still remain the backbone of modern day leukaemia protocols consisting of an induction phase to produce disease remission followed by consolidation and intensification blocks, central nervous system (CNS) directed therapy and continuing therapy to maintain remission.

The mainstay of drug therapy for ALL comprises corticosteroids (prednisolone or dexamethasone), vinca alkaloids (chiefly vincristine), asparaginase, antifolates (methotrexate), anthracyclines (such as daunorubicin) and purine analogues (6-mercaptopurine). Although chemotherapy protocols vary in their exact details between different international trial groups they are broadly comparable. The main phases of treatment are briefly described below.

Remission Induction

Induction therapy aims to eradicate more than 99% of the leukaemic cell burden and restore normal haematopoiesis by the end of 4–6 weeks of therapy. It consists of a combination of corticosteroids, vincristine and asparaginase. These drugs form the
cornerstone of induction because they are non-myelosuppressive, synergistic and target different anticancer pathways. Anthracyclines can be added but these are potentially toxic and myelosuppressive and therefore associated with greater morbidity; for this reason they are often reserved for patients with higher risk disease.

**Consolidation and Intensification**

The next phase of therapy aims to consolidate and/or intensify the treatment to eradicate the remaining 1% or so of leukaemic cells. These cells have survived the original induction therapy and therefore combinations of different anti-leukaemia drugs are used at this stage to try and circumvent drug resistance. There is currently no consensus on the best regimens or their duration but it is generally accepted that ‘stronger not longer’ therapy is best – especially for higher risk disease. This phase of therapy consists of consolidation and delayed intensification blocks and some form of CNS directed therapy. Methotrexate, cyclophosphamide, cytarabine and asparaginase usually play key roles.

**Central Nervous System Prophylaxis**

Soon after the introduction of systemic therapy for ALL it became clear that despite effective bone marrow clearance of disease, up to 75% of children would rapidly relapse with leukaemic blasts in the CNS. To prevent this, treatment was introduced to eliminate leukaemic cells at this site. Initially, this consisted of cranial or craniospinal irradiation, but concerns were raised over the toxic effects of this treatment as discussed below. There has now been a shift to the use of intrathecal chemotherapy and systemic drugs with good CNS penetration in place of radiotherapy without compromising efficacy [1].

**Maintenance Therapy**

The prolonged administration of relatively low dose chemotherapy during a maintenance phase lasting 1–3 years is almost unique to ALL. However, attempts to omit this phase or shorten it below 12 months have led to significantly greater rates of relapse. The reasons why maintenance is required for long-term cure are currently unknown although it may hint at a population of long lived, slow cycling leukaemia-initiating cells. Combinations of oral 6-mercaptopurine (6MP) and methotrexate with or without pulses of vincristine and corticosteroids make up the backbone of this treatment phase.

**Burden of Treatment**

The treatment strategies described above underlie the remarkable improvement in ALL survival rates, but at what cost? The potential for significant long-term sequelae from ALL treatment was first recognised very early on when it became clear that use
of cranial irradiation in young children (particularly those under 2 years of age) could result in significant toxicity. CNS-directed treatment can produce neurocognitive impairment although the precise contributions of systemic chemotherapy, intrathecal treatment and radiotherapy are unclear and most children treated on modern protocols have IQ scores within the normal range [5]. Cranial irradiation is also known to produce a high rate of second malignancies in the CNS as well as significant endocrinopathies. Taken together this has led to removal of cranial irradiation from many current treatment protocols [1].

Major toxicities still occur, both acutely during treatment and as ‘late effects’. The global effects of intensive treatment produce profound immunosuppression leading to an increased risk of death related to fungal and bacterial pathogens (particularly Gram-negative sepsis). In addition, individual therapeutic agents, either alone or in combination, have specific side effects such as avascular necrosis (mainly steroid related), acute pancreatitis (steroids and asparaginase), cerebral venous sinus thrombosis (asparaginase), encephalopathy (methotrexate and cytarabine) and peripheral neuropathy (vinca alkaloids). These toxicities are commoner and more severe in children on more intensive regimens but are also highly age dependent with adolescents suffering many more significant grade 3 and 4 toxicities than younger children.

Taken together, the burden of these individual toxicities is high, particularly in older patients. Toxicity has generally increased over time since advances in supportive care have allowed more intensive scheduling of drugs and uses of higher doses or more potent formulations. Recent ALL trials suggest that in good-risk patients, the risk of treatment-related mortality is approaching the risk of death due to relapsed disease [2]. However, we know that in historical trials with much less intensive protocols, such as the UKALL VII trial which finished in 1980 and only had one block of delayed intensification, approximately 50% of patients were cured. Over the last 30 years progressive intensification of treatment has benefited the remaining 35–40% of patients but at the expense of theoretically overtreating the 50% of patients who would have been cured with less-intensive protocols. These observations have led to a move towards tailored treatment for patients, i.e. reductions in treatment for patients with ‘good-risk’ disease, with the aim of limiting exposure to drugs with the potential for prolonged immunosuppression, major organ toxicity or promotion of secondary malignancy. Conversely identification of patients with poor risk disease may allow further treatment intensification and/or adoption of novel treatment strategies.

Risk Stratification in Childhood ALL

The aim of tailored therapy is to be able to identify prospectively how sensitive the disease (and the patient) will be to treatment and use this information to adjust therapy accordingly. Risk stratification into poor- and standard-risk disease has been used
for many years based on clinical variables such as age and presenting white cell count. More recently, cytogenetic abnormalities have been identified that add to this assessment. The major clinical and biological features in routine use to classify children at initial presentation are discussed below.

Clinical Factors
Age is a major prognostic variable; with children aged 1–9 having consistently better outcomes than infants (aged 0–1) and older children/adolescents. This partly reflects the distribution of different leukaemia cytogenetic subtypes in different age groups (and therefore relates to the leukaemia biologic features discussed below). However, even within a defined subgroup such as Philadelphia positive ALL (Ph+ve ALL) (where the chromosomal translocation t(9;22) is present in the lymphoblasts) children do better than adolescents, who in turn fare better than adults. Interestingly, adolescents treated on adult leukaemia protocols do consistently worse than those treated on paediatric protocols [6] implying that the chemotherapy regimen is an important determinant of outcome.

Presenting white cell count influences prognosis, especially for precursor-B (pre-B) cell disease with counts >50 × 10⁹/l used as the cut off for a higher risk group. Very high white cell counts may produce direct toxicity such as leucostasis, but the reasons behind the adverse prognosis of even moderately elevated white cell counts as a continuous variable are not clear. In T cell disease counts >100 × 10⁹/l are associated with CNS infiltration but lower counts have less prognostic significance.

Biological Features
ALL can be subclassified according to its cell of origin: pre-B, mature B or T cell. Although T cell disease has traditionally fared worse than B cell disease, this prognostic feature has largely been eliminated by modern intensive treatment protocols. In addition, cytogenetic analysis of leukaemic blasts allows identification of acquired genetic abnormalities. Major advances have been made in identifying and understanding the prognostic significance of the myriad chromosomal abnormalities, both numerical and structural found by such analysis [7]. Cytogenetic abnormalities such as the possession of >50 chromosomes per cell (high hyperdiploidy) or the t(12;21) translocation can be good risk, i.e. associated with an excellent outcome with conventional treatment. Others are considered poor risk such as near haploidy (23–29 chromosomes per cell) or presence of a t(4;11) (AF4-MLL) translocation. As seen with many other variables, the high-risk group only accounts for small numbers of patients, so although it is highly predictive of poor outcome in these patients, the majority of relapses occur in the numerically much larger good- and standard-risk groups.

With the sequencing of the human genome and the advent of high throughput technology, an increasing amount of molecular genetic information is becoming available; this is discussed in more detail below.
Identification of a ‘Personalised’ Risk

The clinical and biological risk factors described above are still in widespread use and form the US National Cancer Institute risk stratification used by many trial groups for initial choice of induction therapy (usually 3 vs. 4 drug inductions with addition of an anthracycline for higher risk patients). Although these criteria are reasonably predictive of high- and low-risk disease on a population scale, they are insufficiently sensitive to determine an individual child’s risk of relapse. Indeed, the majority of children fall in the standard risk group and, although their relapse rate is proportionally much lower than high-risk children, they make up numerically the largest group of relapses. Therefore, it would make no sense to globally reduce therapy for standard risk children based on these criteria alone as the number of relapses would inevitably rise.

Another major limitation of standard epidemiological approaches is that the strongest predictor of relapse is the treatment given. With the increased intensity of modern treatment protocols many features that were previously considered high risk, such as male sex and T cell disease, have lost their prognostic significance. Therefore, approaches that take into account the chemotherapy delivered are essential.

Overall, the response to treatment involves interplay between the intrinsic biological properties of individual leukaemic clones, the child’s pharmacogenomic make-up and additional factors such as the exact dose and scheduling of chemotherapeutic agents, compliance with therapy and/or presence of co-existing pathology. This is illustrated in figure 1. These complex and sometimes unmeasurable variables limit the use of risk scores and other algorithms to individualise treatment. Instead, focus has shifted to measuring the end result of all these variables, i.e. the degree of leukaemic cell kill.

Fig. 1. Factors that determine leukaemic cell kill.