Acute Lymphoblastic Leukaemia: A Review

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Acute Lymphoblastic Leukaemia, ALL, is a malignant transformation of lymphoblasts and represents the single commonest type of cancer in the paediatric population. In the United States there are 7000 new cases of paediatric cancer each year and 2100 (30%) of these are ALL.[1] The overall incidence of ALL is 4 per 100,000, the male to female ratio is 1.3:1, and the peak age at presentation is 4 years.[1] The exact aetiology of ALL is still being debated, but there does seem to be some genetic links. The risk of the second of identical twins developing disease in 10 years is 1/6.[1] The risk of ALL in children with Down's syndrome is 1/74 in the first 10 years of life; there is also increased risk amongst those with a congenital immune deficiency, such as ataxia telangiectasia or severe combined immune deficiency.[1] The prevailing theory, currently, is that an insult to the immune system occurring in utero creates cells predisposed to clonal expansion, and that proliferative or infective stress normally encountered in the early years of life causes the actual clonal transformation.[1]

Acute leukaemia usually presents with features that suggest that the bone marrow is not functioning properly (see Table 1). The most common presentation is with fever and/or infection, which just does not seem to clear up; indicating that the immune system is not functioning as well as it might. Anaemic symptoms are also common causes for consultation: the child is pale, lethargic, and easily fatigable. Symptoms of thrombocytopenia may be the reason for presentation: bleeding, which does not stop, easy bruising, or purpuric rash (see result 2). Pressure effects of a filled marrow may cause bone pain, or arthralgia, or abnormal gait.[1] On examination of the child with ALL, lymphadenopathy, hepatomegaly, and splenomegaly are frequently found.[1] As the history which is usually given is fairly non-specific and could be attributable to many things, we cannot diagnose acute leukaemia every time a child with a three week history of lethargy and fever comes in the door; a simple full blood count and peripheral blood film will alert us to the child who needs additional investigations. However these results must be interpreted with care, for there will not always be a report of circulating lymphoblasts to guide us.

Table 1: Frequency of presenting features of ALL

Symptoms		Signs	
fever	61%	lymphadenopathy	63%
bruising	48%	hepatomegaly	61%
anaemia	45%	splenomegaly	57%
bone pain	23%	mediastinal mass	5-10%

The results of the FBC are not always very strikingly suggestive of ALL, but if all the results are considered together then it is usually very straightforward to decide which children require bone marrow examination. If we may consider each result in turn:

1. Erythrocytes: Often there is a normocytic anaemia present. If it occurs in the presence of all other cell lines being normally represented on the blood count, we must search for an inappropriately low reticulocyte count, relative to the level of haemoglobin, to point to the bone marrow as being the problem.

2. Platelets: It is very common for the blood count to show a low platelet count; more than 70% of cases of ALL present with platelet counts of less than 100.[2] The diminished platelet count combined with the history is usually enough to prompt bone marrow investigation.

3. White Cells: The presenting white cell count is of very little help for making the diagnosis of ALL; it may be low, normal, or elevated. There may or may not be abnormal lymphocytes noted on the peripheral blood film, however the differential count will often show an absolute granulocytopaenia (<1,000/ml), especially in those cases where the white count is low, or unremarkable. In the face of a history of infection, which is often the case, granulocytopaenia is unexpected and should prompt further investigation.

Abnormalities in more than one of the three cell lines is a very strong indication, indeed for bone marrow examination, and in most cases of ALL, this is indeed the presentation, making the diagnosis less difficult to make.[2] A bone marrow which contains greater than 25% lymphoblasts can be considered to have acute leukaemia, although some centres set their cut-off level for diagnosis at 10%.[3]

After a bone marrow biopsy has confirmed the diagnosis the treatment phase begins. At this point the cerebrospinal fluid must be examined for any leukaemia infiltration. A central venous catheter must be placed in order to give medicine and transfusions, and to be able to frequently and easily

sample bloods.[1] The first step to treatment, before starting any cytotoxic therapy, is to provide the necessary supportive care. Any infection must be treated with antibiotics that cover both gram positive and gram-negative organisms. Any blood products which are needed should be given: packed red cells if the packed cell volume is less than 20-25%, platelets given if the count is less than 20.[2] The patient must be adequately hydrated, usually with twice maintenance fluids and allopurinol is given to avoid urate nephropathy when the cytotoxic therapy begins.[2]

The definitive therapy of ALL is usually considered in four parts, induction, intensification, CNS prophylaxis, and maintenance treatment. Cotrimoxazole prophylaxis against pneumocystis is also given throughout therapy, and any infection incurred during therapy must be aggressively treated. Induction is the initial phase of treatment, the goal of which is to reduce the leukaemic cell burden as much as possible. In order to achieve this, a combination of several drugs is used to maximize leukaemic cell sensitivity to treatment and increase the efficacy in a synergistic way.[1] The induction phase lasts for 2 weeks, and its success is measured by the amount of leukaemic cells detected in the bone marrow on day 14. If there are less than 5% blasts in the day 14 bone marrow then the induction phase has been successful. This is a good prognostic sign for these patients. If there are more than 5% blasts then the induction has been unsuccessful and a second induction is attempted.[2] Intensification is aimed at reducing to zero the leukaemic cells in the body; it is given at 5 and 20 weeks following induction and again utilizes a multidrug regime to maximize effectiveness. CNS prophylaxis is given to reduce the rate of relapse in the "sanctuary" of the CNS. Prior to prophylactic treatment of the CNS 40% of ALL patients used to relapse in that site. This figure has been reduced to 2-8% with prophylaxis. The current prophylactic regime combines intrathecal administration of methotrexate with cranial irradiation.[1] Maintenance therapy is aimed at preventing relapse without inducing bone marrow aplasia or hypoplasia;[1] it consists of oral cytotoxic therapy and monthly pulses of steroid and vincristine injections given over 2 years. Using this regimen, the 5-year disease free survival for children with ALL is 71%.[4] Of the 30% who die, approximately 5% will succumb during the first treatment[4] and the remaining 25% will die of disease relapse.[2] Those who die during first treatment almost without exception succumb to infection.[4] Those with disease relapse undergo a second induction phase of treatment and should then be referred for allogenic sibling bone marrow transplant while in second remission, if available. If there is no allogenic sibling then heterologous transplantation or chemotherapy is used, but the prognosis for these patients is extremely poor.[5]

In addition to cytotoxic chemotherapy and CNS prophylaxis there is one additional treatment modality available to clinicians in the treatment of ALL: bone marrow transplant. Because of the efficacy of chemotherapy in producing long term cure the role of bone marrow transplant is limited to a very few specific situations. It should be reserved for children with a very small likelihood of cure with chemotherapy.[5] However, this group is difficult to identify, and thus transplantation is reserved for those patients who relapse within 18 months of initial remission,[5] those who relapse after second induction,[6] or those who have the Philadelphia chromosome translocation.[7] The role of bone marrow transplantation is limited to these specific situations because the outlook following transplant as opposed to following chemotherapy is only slightly, if at all, improved.[8]

The treatment regime described is the most efficacious to date in improving long term survival across the spectrum of patients with ALL, but is also associated with several serious side effects. The anthracycline drug, daunorubicin, which they receive in induction and intensification therapy is well known to have cardiotoxic effects, and has been shown to produce left ventricular dysfunction and decreased myocardial growth in the survivors of ALL.[6] The adverse effects of cranial irradiation are well known and have been documented even at the 18Gy level and include: failure to reach growth potential with premature puberty and a diminished pubertal growth spurt,[2] cerebral calcification, neuroendocrinopathies, and central white matter necrosis. These effects manifest themselves in several ways including decreased IQ, lessened academic achievement relative to siblings, 45% of survivors have adult heights less than the 5th centile, 38% are obese with body mass index of greater than 24 kg/m^2.[1] In addition, all patients with ALL have a 2.5% risk of a second neoplasm over 15 years, but those who received irradiation have an 8.1% risk versus 0.3% for those who were not irradiated. The majority of these second tumours are brain tumours in the irradiation field, and the most common type of these is the highly malignant glioblastoma multiforme.[2] Patients receiving the epipodophylotoxins, etoposide or related drugs, are at increased risk of Acute Myeloid Leukaemia (AML).[2]

In order to tailor the best treatment for each child, the paediatric oncology group (POG) has suggested that treatment of children with ALL be along two different courses, a standard risk protocol and a high-risk protocol.[3] The determination of which group a particular patient falls in to is based on several criteria:

1. Age: The standard risk group falls between ages 1 to 10 years. Any patient outside of this range must be treated aggressively with the high-risk protocol.

2. White cell count at presentation: The standard risk category is given to patients with a

Table 2: *The Prognostic Indices* [1]

Good prognosis	Bad prognosis
age 2-9 years	age <1 year or >10 years
initial WCC<10	initial WCC>50
initial platelet >100	initial platelet <100
>50 chromosomes without structural abnormalities	t(9;22), t(4;11), t(1;19)
<5% blasts on the day 14 marrow	>25% blasts on day 14

count of less than 50,000/ml, patients with higher counts are at increased risk.

3. CNS disease: The presence of CNS disease at presentation is a poor prognostic sign and therefore warrants more aggressive treatment.

4. Immunophenotype of disease: Children with B precursor cells have the best prognosis, those with T-cells have risk determined by their age and white cells at presentation, those with mature B cells are immediately placed in the high risk group.

5. Presence of translocations: If the clone of malignant cells contains any of the following chromosomal translocations a patient is immediately considered high risk. The Philadelphia chromosome, t(9;22), is a particularly ominous sign and requires very aggressive therapy. The other translocations which are high risk are t(4;11) and t(1;19).[1]

6. Cytogenetic studies: The karyotype of the clone of cells is also of prognostic significance. If the clone is near haploid then the prognosis is poor and more intensive treatment should be given. However if the clone is hyperdiploid, showing more than 50 chromosomes, these patients have an improved prognostic outlook, if all other things are equal. If the extra chromosomes show trisomy of both chromosome 4 and 10 this improves the outlook even more.[7]

The current recommendation from the POG and other researchers suggests that those children in the standard risk group may be treated effectively with a less intensive regime. The protocol currently under investigation is that in the good prognosis group that induction may be achieved with prednisolone, vincristine and L-aspariginase[3] combined with intrathecal methotrexate, cytarabine and hydrocortisone.[10] Under this regimen the cardiotoxic anthracycline is removed, and the epipodophylotoxins which predispose to acute leukaemia are eliminated, and all of the adverse effects attributed to cranial irradiation can be avoided. In addition, the use of a less intense treatment regime initially will allow a better retrieval of those patients who do relapse, because a greater range of more intensive therapies will be available to treat the patient, instead of relying solely on repeating the same combination approach attempted originally,[2] this must be balanced against the fact that less patients relapse when treated originally with the more intensive regimen.[2] While these arguments are convincing that a less intensive regime is a very attractive alternative, it remains to be proven that this protocol will be as effective in providing long-term disease free survival and cannot be recommended until such time.

The treatment of ALL has advanced incredibly in the last forty years, from a universally fatal disease to one where the treatment is now being tailored away from improving the survival outlook to improving the quality of life of the children when they survive. This is certainly one of the greatest success stories in the treatment of malignancy and gives us a model to work from for the treatment of all cancer, and hope to conquer malignancy in the future.

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