

Acute Lymphocytic Leukemia in Children

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Detailed discussions of acute lymphocytic leukemia (ALL) in childhood are available in the standard texts of hematology.⁽¹⁾ In this paper the purpose will be to review the new information of the last two years in consideration of etiology, risk factors for prognosis and treatment assignment, the disease in infancy, current treatment approaches, the problem of relapse, and the late consequences of the disease and its treatment. It is tempting to deal also with the growing information about the molecular biological aspects of the disease and its implications for the clinical features and response to therapy. However, it would take a separate paper to do that topic justice.

Etiology

It has long been known that there are geographical differences as to the incidence of the disease and that there has been a striking change in incidence among children in some countries since the middle of this century.⁽²⁾ These observations clearly suggest environmental factors that influence the risk of this disease. However, in spite of the great deal of attention in the lay press that has been given to electromagnetic forces, parental exposure to irradiation, and the eating of processed meats, a recent careful study in Sweden⁽³⁾ identified known factors such as Downs' syndrome and a few maternal and perinatal associations, but overall the authors concluded that most risk factors for childhood lymphocytic leukemia remain unidentified. Recently, it has been observed that acute lymphocytic leukemia occurring in infant twins was clonal, with an identical rearrangement of chromosome band 11q23 occurring in the leukemia cells in each twin.⁽⁴⁾ Because the immunoglobulin genes were not identical in the cell populations of the two twins, the authors speculated that the malignant transformation had taken place in a B-cell precursor in one twin and then populated the blood of both. This gene rearrangement is a common feature of infant leukemia, and this observation suggests that infant leukemias bearing this genetic marker arise in utero. Since this genetic change is also a marker for the leukemias induced by exposure to etoposide given as treatment for ALL, in utero exposure to a similar compound could be the responsible event.

Risk Factor Assessment

By 1970 it was evident that about 50 percent of children treated for ALL could be expected to be long-term survivors. During the decades that have followed, many clinical and laboratory features have emerged that identified patients more or less likely to have a favorable response to treatment. This assignment to a risk category is important for several reasons. It is obviously important to the individual patient and the family. It is helpful to the clinician in assigning the child to a treatment program of either lesser or greater intensity. It is also critical in clinical therapeutic studies so that results from different institutions and groups can be compared. Finally, sometimes it may be important

for etiological considerations for, as noted above, specific biological features may be associated with specific etiological factors.

Recently, a workshop was held to develop a uniform approach to risk classification and treatment assignment.⁽⁵⁾ A simple classification was developed where standard risk was considered to be a white blood count less than 50,000 per microliter and an age of between one and ten years. In that group, 80 percent achieved a four-year event-free survival. The high-risk group represented white blood counts greater than 50,000 per microliter or an age greater than ten years; in this group, about 64 percent achieved a four-year event-free survival. The workshop recommended that other prognostic factors be uniformly collected and reported. These factors included DNA index, rate of response to therapy, cytogenetics, immunophenotype, and the presence of central nervous system disease. A hyperdiploid karyotype with a DNA index greater than 1.16 may have a favorable prognosis because of a greater sensitivity to antimetabolites and other drugs.⁽⁶⁾ Response to therapy can be determined by bone marrow findings at day 14 of induction, but even more information may be obtained by determining the marrow status on day seven,⁽⁷⁾ and persistence of circulating blasts after one week of treatment confers a poor prognosis.⁽⁸⁾ With respect to cytogenetics, the workshop confirmed the extremely bad prognosis of the chromosomal locations involving t(9;22) and t(4;11). It was regarded that these findings put a child in the high-risk group regardless of other clinical or laboratory features. Immunophenotyping should be done in all cases, but there is some disagreement as to the prognostic implications of a T-cell immunophenotype, which some groups regard to have a poor prognostic implication. Others feel that, with current therapy, the T-cell immunophenotype alone should not be regarded as a high-risk feature. The subject has been recently reviewed.⁽⁹⁾

The presence of overt CNS disease at diagnosis is regarded as a poor prognostic feature, with implications both for bone marrow relapse as well as CNS relapse. It clearly indicates a more aggressive approach to CNS treatment. It is regarded that low numbers of CSF blasts at diagnosis do not carry the same significance as overt disease.⁽¹⁰⁾ This has been a somewhat controversial point, but a consensus now seems to have been reached that, if the spinal fluid count is less than five cells per microliter, no additional prognostic information is present.

ALL in Infancy

Acute leukemia in infancy has an equal distribution of lymphoid and myeloid subtypes. The clinical features have been recently reviewed.⁽¹¹⁾ The clinical features include a cluster of bad prognostic features such as high white blood counts, massive hepatosplenomegaly, and an increased frequency of CNS overt leukemia. Phenotypically, almost all lymphoid leukemias are B-cell precursor in type. A specific cytogenetic characteristic involves translocations at 11q23 with rearrangements of the HRX (MLL) gene.^(12,13) Even if the translocation is not evident on karyotype, it can be found by demonstrating the molecular rearrangement of this gene on Southern blot.⁽¹³⁾ In this manner 80 percent of infant ALL patients have this rearrangement. As indicated above,⁽⁴⁾ this genetic damage most certainly occurs in utero, perhaps related to exposure to a plant product such as etoposide or some other carcinogen. The remission rate with therapy is

quite good, being about 90 percent. However, the relapse rate is high and event-free survival at four years can be expected to be about 20 to 30 percent. There are no current reports of clinical trials for ALL in infants that give promise of better results.

Treatment

The results of several large single-institution and multi-institution studies have recently been published.⁽¹⁴⁻¹⁷⁾ Current studies involve stratification of patients by risk groups as discussed above with more intensification of therapy going to those with higher risk features, with efforts to reduce treatment intensity in children with standard risk features to avoid chemotherapy-induced late consequences. Each of the reports varies in the details of drug sequences, scheduling, and doses, but the basic outline is similar. Following multidrug remission induction, most current therapies include a post-induction period of intensification. CNS prophylaxis⁽¹⁸⁾ has included cranial irradiation at 18 Gy⁽¹⁵⁾ or intrathecal methotrexate⁽¹⁹⁾ for standard risk leukemia. For those children at high risk for CNS relapse, 24 Gy have been used.⁽¹⁵⁾

The role of drug dose in event-free survival, especially for such antimetabolites as methotrexate, has been documented.⁽²⁰⁾ Recent in vitro studies of methotrexate and 6-mercaptopurine metabolism^(21,22) have provided further evidence for the rationale of higher doses of the antimetabolites. Further studies should be done to determine if dose modification to achieve the metabolic effects associated with better response are needed and may allow for the individualization of treatment to the pharmacokinetic characteristics of the patient. The treatment of very high risk ALL such as that characterized by the Philadelphia chromosome has been attempted with intensive early chemotherapy followed by rotational treatment with pairs of non-cross resistance drugs.⁽²³⁾ This approach may allow for long-term, event-free survival for a few patients.

Relapse

Relapse is associated with the acquisition of drug resistance in the leukemic blasts.^(24,25) It is possible to monitor the bone marrow for minimal residual disease using molecular techniques.⁽²⁶⁾ For acute lymphoblastic leukemia, the probe most often used is the clonal rearrangement of immunoglobulin or T-cell receptor gene rearrangements. This approach must be done with care because of the genetic progression in the leukemic cell population and the possibility of the emergence of new genetic subclones bearing different molecular markers.^(27,28) Furthermore, the utility of early identification of a resistant population of cells has not yet been demonstrated.

Treatment of a bone marrow relapse has been attempted with both chemotherapy and allogeneic bone marrow transplantation.⁽²⁹⁾ The relapse having the worst prognosis is one that occurs either during therapy or early after the cessation of therapy. It may be that an allogeneic bone marrow transplantation provides a better result in this case. There is no evidence, however, that bone marrow transplantation is superior to reinduction and treatment with chemotherapy alone for those patients relapsing late after cessation of therapy. A CNS relapse necessitates an intensive retreatment protocol, even if the relapse is isolated to the central nervous system.⁽³⁰⁾ Treatment of the isolated CNS relapse in

addition to systemic chemotherapy involves intrathecal chemotherapy and cranial/spinal irradiation.

Late Consequences of Disease and Treatment

Children successfully treated for ALL and apparently cured must continue to be followed, perhaps for a lifetime, to observe for the development of late secondary consequences of the disease and its treatment. Perhaps the most important of these consequences are those related to CNS prophylaxis.⁽³¹⁾ Much has been written about cognitive changes following treatment for ALL and much remains to be learned. Certainly there is interaction of cranial irradiation with chemotherapeutic agents such as methotrexate given in high doses. There is indication that lowering the cranial irradiation dose from 24 Gy to 18 Gy has reduced the likelihood of CNS effects. The same claim is made for those children treated with intrathecal chemotherapy alone. Children treated with current protocols need continued evaluation of CNS status so that the likelihood of relapse is minimized with the least possible, if any, effect on the CNS. The range of late effects is wide. The growth pattern may be disturbed with both growth retardation and obesity as late consequences.⁽³²⁾ Growth retardation certainly may be an effect of treatment, especially cranial irradiation on growth hormone production. The mechanism for obesity is a little more subtle and may involve psycho-social changes associated with the disease and its treatment and the effect on the child and family. As in other malignancies associated with potentially mutagenic therapy, second primary malignancies occur in survivors of the treatment of ALL.⁽³³⁾ The actuarial risk of a second malignancy 25 years after treatment has been calculated as five to six percent. Chronic infections such as hepatitis C virus may be acquired by children during the therapy and result in longstanding chronic inflammatory disease.⁽³⁴⁾ Because of the immunosuppression, hepatitis C antibody reactivity may not be demonstrable, and molecular identification of the virus by sensitive techniques may be necessary. Obviously, children with ALL are at risk for all of the transfusion related infections, which may occur even in the face of rigorous blood bank screening. Since our experience with long-term survivors of childhood ALL is only about three decades old, careful studies must be done to thoroughly describe the possible late events that might occur. Furthermore, therapy is continually evolving and unexpected results such as the unanticipated early onset acute myeloblastic leukemia following etoposide or teniposide may be found.

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