

EDUCATION SESSION 1: TREATMENT OF ACUTE LEUKEMIA



Treatment of Childhood Acute Lymphoblastic Leukemia

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Contemporary treatments now cure at least 70% of children with acute lymphoblastic leukemia (Table 1).¹⁻¹² This achievement can be credited largely to more effective multidrug regimens evaluated in well-designed clinical trials. Because ALL is a heterogeneous disease with many distinct subtypes, a uniform approach to therapy is never satisfactory for all patients. Instead, current emphasis is placed on “risk-directed” therapy in strategies to avert both under- or over-treatment of patients with newly diagnosed leukemia. There remains, however, considerable disagreement over the optimal combination of risk factors for establishing prognostically important subgroups. Here we provide ra-

tionales for three risk categories—low, standard (average) and high—including examples of treatment advances in each.

Risk Assessment

Clinical Factors

Treatment remains the single most important prognostic factor in childhood ALL. Many presenting clinical and biologic variables have emerged as useful prognostic indicators over the past two decades, only to disappear as treatment has improved.¹³ Age and leukocyte count, which have

Table 1. Current Results of International Studies of Childhood ALL

Study	No. of Children	Event-Free Survival Rate (±SE) %	Reference
AIEOP ALL 91 (1991-1995)	1189	≈71 at 5 y	Putti ¹
ALL/BFM/HPG'90 (1990-1995)	374	64 (5) at 5y	Sackmann-Muriel ²
BFM 90 (1990-1995)	2178	78 (1) at 5 y	Schrappé ³
CCG 1800 series (1988-1995)	3937	70.7 (0.9) at 7 y	Uckun ⁴
CCLSG ALL911 (1991-1993)	223	70 (3) at 7 y	Tsurusawa ⁵
Dallas/Fort Worth (1986-1992)	243	66.6 (7) at 5 y	Winick ⁶
DFCI 9109 (1991-1995)	377	84 (4) at 4 y	Silverman ⁷
Dutch VI (1984-1988)	291	72 (3) at 6 y	Veerman ⁸
FRALLE 89 (1989-1992)	586	55.6 (2.2) at 5 y	Donadieu ⁹
POG AlinC14 & 15 (1986-1994)	3825	≈71 at 5 y*	Shuster ¹⁰
SJCRH XIII A (1991-1994)	165	80.2 (9.2) at 5 y	Pui ¹¹
UKALLXI (1990-1995)	1689	74 – 76 at 3 y	Lilleyman ¹²

Abbreviations:

AIEOP – Associazione Italiana Ematologia Oncologia Pediatrica;
BFM – Berlin Frankfurt-Münster;
CCG – Children's Cancer Group (Arcadia, CA);
CCLSG – Children's Cancer and Leukemia Study Group (Japan);
Dallas/Fort Worth (TX);
DFCI – Dana-Farber Cancer Institute/Children's Hospital Acute Lymphoblastic Leukemia Consortium (Boston, MA);

Dutch – Dutch Childhood Leukemia Study Group;
FRALLE – French Acute Lymphoblastic Leukemia Cooperative Group;
HPG – Hospital de Pediatria Garrahan (Buenos Aires, Argentina)
POG – Pediatric Oncology Group (Chicago, IL); AlinC – Acute Leukemia in Childhood (protocol);
SJCRH – St. Jude Children's Research Hospital (Memphis, TN);
UKALLXI – United Kingdom Acute Lymphoblastic Leukemia XI.

*Excluding T-cell, t(4;11) and t(9;22) cases.

consistent prognostic impact in B-cell-precursor ALL, are exceptions. In general, age between 1 and 9 years and a leukocyte count of less than $50 \times 10^9/L$ are used to define low-risk cases of B-cell-precursor ALL.¹⁴ Gender is another consistent clinical factor with prognostic implications. In virtually all clinical trials, boys have fared worse than girls given equivalent therapy.^{10,15} The overall poorer prognosis of boys can be explained in part by their higher incidence of T-cell ALL and lower incidence of a favorable DNA index.¹⁵ In this regard, a significant gender difference in treatment outcome was observed among cases of B-cell-precursor ALL cases treated at our institution, but we were not able to identify any biologic or pharmacologic explanation for this finding. Thus, many investigators have opted to treat boys with extended continuation therapy (i.e., 3 years instead of 2 to 2½ years as in girls) in an attempt to reduce the gap in survival between the two sexes. Whether this strategy will increase the proportion of male survivors will not be clear until the completion of several ongoing clinical trials.

Genetic Features

Among the biologic factors studied to date, specific genetic abnormalities (found in the leukemia cells of 75% of patients) have been the best predictors of treatment outcome,¹³ Hyperdiploidy (>50 chromosomes) and *TEL-AML1* (*ETV6-CBFA2*) gene fusion confer a favorable prognosis in ALL, whereas hypodiploidy (<45 chromosomes), *BCR-ABL* fusion (Philadelphia chromosome, Ph) and *MLL-AF4* fusion [t(4;11)] are associated with a poor prognosis. Even so, there is some clinical heterogeneity within the subgroups defined by these alterations. For example, as many as 20% of children with so-called favorable genetic features will eventually relapse, while approximately a third of those with high-risk abnormalities can be cured with intensive chemotherapy alone. Among hyperdiploid cases, patients with higher modal chromosomal numbers (56 to 67 chromosomes) appear to fare better than those with 51 to 55 chromosomes per leukemic cell.¹⁶ We and others have shown that the subsets of Ph+ cases with low presenting leukocyte counts or good initial response to prednisone therapy are curable with intensive chemotherapy.^{17,18} The prognosis of *MLL-AF4* or *MLL-ENL* [t(11;19)(q23;p13.3)] fusion depends largely on age; children 1 to 9 years of age have a significantly better outcome than do infants or older children.¹⁹⁻²² Interestingly,

MLL-ENL fusion can be found in both B-lineage and T-lineage ALL, the latter being associated with an excellent prognosis.²²

In-Vivo Drug Sensitivity

The drug sensitivity of leukemic cells early in the clinical course is another useful predictor of treatment outcome, regardless of cell lineage. The efficacy of early treatment can be readily assessed by analyzing the clearance of circulating or bone marrow blasts after single agent or combination induction treatment.²³ Recently, measurement of the level of minimal residual leukemia by either flow cytometry or polymerase-chain-reaction amplification of clone-specific immunoglobulin and T-cell receptor gene rearrangement has been shown to improve risk assessment.²⁴⁻²⁶ Approximately 20% of patients who failed to attain an “immunologic” or “molecular” remission, defined as leukemic involvement of less than 0.01% of bone marrow mononuclear cells after induction therapy, were found to have a high relapse hazard, regardless of their presenting features. Hence, we have now incorporated the assessment of early treatment responsiveness—i.e., the percentage of bone marrow blasts on day 19 of remission induction and the level of minimal residual leukemia on day 46 (end of induction therapy)—into our risk classification system (**Table 2**). Whether an increase in the intensity of postremission therapy will improve long-term outcome in patients with a poor early treatment response remains to be determined. In this regard, recent improvement of treatment outcome in the BFM90 protocol was largely confined to patients with a good early response to prednisone.³

Advances In Risk-Directed Therapy

Early Intensification of Systemic Chemotherapy

With improvements in chemotherapy and supportive care, the rate of complete remission now ranges from 97% to 99%. Current efforts to intensify induction and consolidation therapy is driven by the premise that more rapid and more extensive complete reduction of the leukemic cell burden will forestall the development of drug resistance. **Table 3** summarizes several treatment strategies that have had a particularly marked effect on clinical outcome. Dexamethasone, when used in induction and continuation regi-

Table 2. Risk Classification System in St. Jude Total Therapy Study XIV

Risk Group	Feature
Low	B-cell precursor phenotype with age 1-9 years and presenting leukocyte count $<50 \times 10^9/L$; <i>ETV6-CBFA2</i> fusion; or hyperdiploidy >50 (DNA index >1.16 and <1.60) Must not have (i) CNS leukemia (CNS-3 status) (ii) testicular leukemia, (iii) t(9;22), (iv) t(1;19), (v) rearranged <i>MLL</i> , (vi) hypodiploidy or (vii) poor early response*
Standard	T-cell ALL and all cases of B-cell precursor ALL not meeting the criteria for low- or high-risk ALL.
High	t(9;22)(<i>BCL-ABL</i>) with leukocyte $>25 \times 10^9/L$ or poor early response; rearranged <i>MLL</i> gene with age <12 months; or induction failure.

* $>5\%$ blasts in bone marrow on day 19 and/or $<0.01\%$ blasts on day 46 of remission induction.

mens, has provided better control of systemic and CNS disease than does prednisone,^{7,8,27} perhaps because of its increased penetration into cerebrospinal fluid and its longer half-life. Several forms of L-asparaginase, each with a different pharmacokinetic profile, are available. Patients treated with *Escherichia coli* L-asparaginase have a better outcome than those receiving the same dosage of *Erwinia carotovora* L-asparaginase,²⁸ which has a shorter half-life in plasma. Indeed, the excellent long-term results coming from several different clinical trials can be attributed to the intensive use of L-asparaginase during the early phase of postremission therapy.^{7,29} However, even among different preparations of *Escherichia coli*, one can find variable pharmacologic and pharmacokinetic properties, mandating dosage adjustment to avoid excessive toxicity.^{30,31}

High-dose methotrexate is perhaps the most common form of consolidation chemotherapy used in childhood ALL. Given at 1 g/m², methotrexate produced better results than did fractionated lower doses of the same drug (30 mg/m² every 6 hours orally for 6 doses) in a study of patients with B-cell precursor ALL.³² Very high doses of methotrexate (5 g/m²) appeared to improve clinical outcome in patients with T-cell ALL,³³ consistent with data indicating that T-lineage blast cells accumulate methotrexate and its active polyglutamate metabolites less avidly than do B-lineage lymphoblasts.³⁴ Thus, higher serum concentrations of methotrexate are needed for adequate accumulation of these compounds. Indeed, we have shown that the conventional dose of methotrexate 1 g/m² may be too low for many patients with B-cell precursor ALL,³⁵ and that increased system exposure to methotrexate could improve clinical outcome in this subgroup.³⁶ Also, high-dose cytarabine may selectively improve outcome in T-cell ALL and infant ALL.³⁶⁻³⁸ In fact, in two German multicenter trials in adults, the use of high-dose cytarabine and mitoxantrone has markedly improved results in cases with the t(4;11),³⁹ which defines the most common genetic subtype of infant ALL.

Optimization of Continuation Therapy

While methotrexate and 6-mercaptopurine are standard components of continuation therapy for childhood ALL, other agents can be used to improve the efficacy of such treatment. One example is the use of intermittent pulses of vincristine and a glucocorticoid,⁴⁰ a strategy now widely

adopted in continuation protocols. Many centers also rely on reinduction therapy generally introduced in the first 4 to 6 months of continuation therapy. This approach, which relies on the same drugs used during the initial phase of induction therapy, has been shown to improve outcome not only in high-risk patients, but in standard-risk and low-risk patients as well.^{33,41,42} Prolonged intensification including a second reinduction phase or rotational administration of ostensibly non-cross-resistant drug pairs may further improve outcome in patients with standard- or high-risk ALL.^{29,43} A recent study at our institution showed that the dose intensity of 6-mercaptopurine, defined as the number of weeks a drug is given relative to the number of protocol-specified doses, is the single most important pharmacologic factor influencing treatment outcome.⁴⁴ Antimetabolite treatment should not be withheld because of isolated elevations of liver enzymes, which appear to lack any long-term consequences.⁴⁵ However, overzealous use of 6-mercaptopurine, such that neutropenia precludes chemotherapy administration, is counterproductive.⁴⁴ Hence, our data support a balanced approach to dosage individualization in childhood ALL.

Early and Intensive Intrathecal Treatment

Concern that cranial irradiation may cause late neurologic sequelae and occasional brain tumors has led many leukemia therapists to replace this modality with intensive intrathecal and systemic chemotherapy. This approach, together with cranial irradiation to high-risk cases, has lowered the rate of CNS relapse to approximately 1%, in turn boosting the overall 5-year event-free survival rate to 80%.¹¹ Whether certain groups of patients at high risk of relapse should be treated with cranial irradiation is uncertain. In one retrospective study, children with T-cell ALL and leukocyte counts <100 x 10⁹/L had similar outcomes whether or not they received cranial irradiation; however, among those with higher leukocyte counts, the irradiated group had better long-term responses than did patients given intrathecal chemotherapy alone.⁴⁶ These results are not conclusive because systemic chemotherapy was more intensive in the irradiated group. This uncertainty notwithstanding, a radiation dose as low as 12 Gy, together with effective systemic chemotherapy, appeared to provide adequate protection against CNS relapse, even in high-risk patients.⁴⁶ Both the St. Jude and Dutch groups are now testing the hypothesis

Table 3: Treatment Strategies Associated with Improved Outcomes

Strategy	References
Dexamethasone treatment	Silverman ⁷ ; Veerman ⁸ ; Bostrom ²⁷
Intensive asparaginase treatment	Silverman ⁷ ; Nachman ²⁹
High-dose methotrexate	Mahoney ³² ; Reiter ³³ ; Evans ³⁵
Increased systemic exposure to methotrexate	Evans ³⁶
High-dose cytarabine	Evans ³⁶ ; Silverman ³⁸
Reinduction and re-consolidation therapy	Nachman ²⁹ ; Reiter ³³ ; Tubergen ⁴¹ ; Chessells ⁴²
Increased dose intensity of 6-mercaptopurine	Relling ⁴⁴
Early and intensive intrathecal treatment	Pui ¹¹

that cranial irradiation can be omitted for all patients, regardless of their risk features.

Future Considerations

New antileukemic agents are needed to treat ALL refractory to currently available drugs. Arabinosylguanine has shown considerable promise against resistant T-cell ALL, inducing complete remission in almost half of the patients that were initially refractory to therapy or subsequently relapsed.^{47,48} Targeted immunotherapy, gene therapy and antiangiogenic treatment may ultimately have a therapeutic role in ALL.¹³

Pharmacogenetics represents another permutation of genetic studies with clinical implications. Recognition of inherited differences in the metabolism of selected antileukemic agents has made it possible to accurately identify patients who are at high-risk of toxicity, thereby providing a rational way of selecting optimal drug dosages or scheduling. This point is well illustrated by the study of thiopurine methyltransferase, a cytosolic enzyme that inactivates 6-mercaptopurine and 6-thioguanine. Patients with a deficiency of this enzyme are at risk for severe hematologic toxicities when treated with standard doses of thiopurines and the development of epipodophyllotoxin-related acute myeloid leukemia or irradiation-induced brain tumors.^{49,50} Molecular methods based on genomic DNA are now available for the diagnosis of this deficiency.⁵¹ Similar studies of other anticancer drugs known to be substrates for polymorphic enzymes should provide additional guidelines for increasing the efficacy or decreasing the toxicity of antileukemic therapy.

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