The incremental increase in survival among children with acute lymphoblastic leukemia over the past 50 years is often cited as the great success story in clinical oncology. Leukemias are the most common malignancy of childhood, with an annual incidence of 40 cases per 1,000,000 people in the US, accounting for a quarter of all childhood malignancies. In the US, more than 3,000 children are diagnosed with leukemia each year, 80% of which are acute lymphoblastic leukemias (ALL).

The peak incidence of childhood leukemia is approximately four years of age, although this peak is due almost entirely to patients diagnosed with ALL. Acute myelogenous leukemia (AML) is equally distributed among patients aged 0–10, with a slight increase in incidence in adolescence. ALL is more common among whites than blacks in the US, but AML has an equal distribution among all ethnic groups. The incidence of leukemia is also slightly higher among boys than girls. The ratio of boys with leukemia to girls with leukemia is greatest during adolescence, particularly in the subset of patients with T-cell ALL.

The exact cause of most leukemias is still not known, although there are a number of predisposing factors and exposures. In all likelihood, the cause or causes of most leukemias is multifactorial, including genetic, immune, infectious, and environmental factors.

Clinical Manifestation

The presenting clinical features of the acute childhood leukemias reflect the uncontrolled proliferation of malignant cells leading to replacement and suppression of normal hematopoietic progenitor cells, and infiltration into extramedullary spaces. Symptoms frequently accumulate in a matter of days or weeks, culminating in some event that brings the child to medical attention. Chronic Myelogenous Leukemia (CML) may present with a more insidious course. The differential diagnosis of an acute leukemia at presentation is included in Table 3.

Classification

ALL is the most common form of leukemia in childhood (see Figure 1). Subclassification into early pre-B-cell, pre-B-cell, B-cell, and T-cell lymphoblastic leukemias is essential to treatment, and prognostic stratification of patients. The myeloid leukemias can be categorized according to either the cell of origin (French-American-British, FAB, system) or cytogenetic and morphologic features (WHO (World Health Organization) Classification system). The distinguishing phenotypic features of each class of leukemia is listed in Table 4.

Cytogenetic and Molecular Markers

There are several well-described genetic mutations that not only offer insight into the pathogenesis of an acute leukemia, but which significantly influence prognosis.

Treatment of ALL

Risk-Stratified Therapy

Risk-adapted therapies, taking into account clinical features (age, white blood cell count, and response to induction therapies) and biologic features (ploidy and mutations of known prognostic significance), are used to maximize cure rates while minimizing long-term side effects. Standard risk and high-risk patients are initially distinguished based on age (between 1 and 9.99 years of age is standard risk) and the initial white blood cell count ($50,000/µL is standard risk). Other clinical features used to stratify therapy include gender, leukemia phenotype, cytogenetics, and response to initial therapy.
three drugs (vincristine, asparaginase, and a corticosteroid) in standard risk patients, or four drugs in high risk patients (the same three as in standard risk patients with the addition of daunorubicin). The goal is to induce a complete remission, defined as the reduction the leukemia cell burden below clinical, morphological, and molecular levels of detection after recovery of normal blood counts. With current chemotherapeutic regimens, remission induction is possible in more than 95% of children with ALL. Many protocols follow the induction phase, with a consolidation phase heavy in antimetabolites to secure or consolidate the remission. Stratification to higher or lower intensity therapies may occur at the end of induction based on molecular quantification of minimal residual disease.

Delayed intensification is a second phase of intensified chemotherapy similar to the induction and consolidations phases. The addition of a delayed intensification phase by the Berlin-Frankfurt-Munich (BFM) group has led to significant improvement in survival in all childhood ALL patients. Survival among patients with high-risk leukemia may be further improved by augmenting the regimen with a second delayed intensification.

In the past two decades, several trials have demonstrated that central nervous system (CNS) radiation may be reduced (to 1200cGy to 1800cGy) or eliminated in patients with low-risk B-cell ALL with a rapid early response to induction therapy. Elimination of cranial radiation in patients with T-cell ALL has not proven feasible. Reduction in cranial radiation is designed to reduce long-term endocrine and cognitive effects, as well as reduce the risk of secondary malignancies.

Unlike treatment paradigms for most malignancies, successful therapy for childhood ALL includes a protracted maintenance period. Attempts to reduce therapy to less than 24 months have never been successful. In current Children’s Oncology Group (COG) Studies, boys with standard risk ALL receive three years of post-remission therapy, while girls with ALL receive two years of post-remission therapy. The intensity of therapy is greatly reduced during maintenance, and many patients may return to school during this period.

Infant ALL

Despite intensified therapy, infants less than six months of age with ALL have an event-free survival of less than 10%, while those older than six months have an event-free survival of 40%. Currently, all infants still have a higher incidence of relapse, death from toxicity, and long-term side effects when compared to older children.

Table 1: Factors Associated with a Higher Risk of Developing Leukemia

<table>
<thead>
<tr>
<th>Environmental Exposures</th>
<th>Genetic Predisposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionizing radiation (therapeutic or environmental exposure)</td>
<td>Siblings of patient with a childhood leukemia</td>
</tr>
<tr>
<td>Etopodophyllotoxin or alkylator-based chemotherapy</td>
<td>Down syndrome</td>
</tr>
</tbody>
</table>

Table 2: Common Clinical and Laboratory Findings Present at Diagnosis in Children with Leukemia

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>ALL (%)(176)</th>
<th>AML (%)(177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>61</td>
<td>34</td>
</tr>
<tr>
<td>Pallor</td>
<td>55</td>
<td>25</td>
</tr>
<tr>
<td>Petechiae, purpura, bleeding</td>
<td>48</td>
<td>33</td>
</tr>
<tr>
<td>Anorexia or weight loss</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>Fatigue, malaise</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Bone, joint pain</td>
<td>38</td>
<td>18</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>68</td>
<td>55</td>
</tr>
<tr>
<td>Swollen gingivae</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Cough, dysphagia</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Recurrent infection</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory Features</th>
<th>ALL (per mm³)</th>
<th>AML (per mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>&lt;10,000</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>10,000–49,000</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>&gt;50,000</td>
<td>17</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>&lt;7</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>7–11</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>&gt;11</td>
<td>12</td>
</tr>
<tr>
<td>Platelet count (per mm³)</td>
<td>&lt;20,000</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>20,000–99,000</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>&gt;100,000</td>
<td>25</td>
</tr>
</tbody>
</table>

In pediatric relapsed or refractory ALL respond with Clolar®

Clolar® is indicated for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.

Tolerability

Clolar should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Suppression of bone marrow function, which is usually reversible and dose dependent, should be anticipated and is likely to increase the risk of infection, including severe sepsis. Administration of Clolar results in a rapid reduction in peripheral leukemia cells. Patients should be evaluated and monitored for signs and symptoms of tumor lysis syndrome and cytokine release (e.g., tachypnea, tachycardia, hypotension, pulmonary edema) that could develop into systemic inflammatory response syndrome (SIRS)/capillary leak syndrome, and organ dysfunction. Clolar should be discontinued immediately in the event of clinically significant signs or symptoms of SIRS or capillary leak syndrome, either of which can be fatal, and use of steroids, diuretics, and albumin considered.

The most common adverse effects after Clolar treatment, regardless of causality, were gastrointestinal tract symptoms, including vomiting (grade 3: 8%; grade 4: 1%), nausea (grade 3: 15%; grade 4: 1%), and diarrhea (grade 3: 10%); hematologic effects, including anemia (grade 3: 70%; grade 4: 18%), leukopenia (grade 4: 9%), thrombocytopenia (grade 3: 36%; grade 4: 64%); and febrile neutropenia (grade 3: 53%; grade 4: 3%). Infection (grade 3: 56%; grade 4: 18%)

Hepato-biliary toxicities were frequently observed in pediatric patients during treatment with Clolar. The most frequently reported cardiac disorder was tachycardia (34%), which was, however, already present in 27.4% of patients at study entry. Left ventricular systolic dysfunction was also noted. Since Clolar is excreted primarily by the kidneys, drugs with known renal toxicity should be avoided during the 5 days of Clolar administration. In addition, since the liver is a known target organ for Clolar toxicity, concomitant use of medications known to induce hepatic toxicity should also be avoided.

Severe bone marrow suppression, including neutropenia, anemia, and thrombocytopenia, have been observed in patients treated with Clolar. Because of the pre-existing immuno-compromised condition of these patients and prolonged neutropenia that can result from treatment with Clolar, patients are at increased risk for severe opportunistic infections.

Pericardial effusion was a frequent finding in these patients on post-treatment studies. Careful hematologic monitoring during therapy is important. Hepatic and renal function should be assessed prior to and during treatment with Clolar, as the liver is a target organ for Clolar toxicity and the kidneys are the predominant mode of Clolar excretion.

Patients receiving Clolar may experience vomiting and diarrhea; they should therefore be advised regarding appropriate measures to avoid dehydration. Clolar may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant and avoid breastfeeding while receiving treatment with Clolar.

Please see brief summary of full prescribing information on adjacent page.

Respond now.
800-RX-CLOLAR or visit www.clolar.com

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INDICATIONS AND USAGE
CLOLAR® is indicated for the treatment of pediatric patients 1 to 21 years old with refractory acute lymphoblastic leukemia after at least two prior regimens. This use is based on single-arm studies. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.

CONTRAINDICATIONS
None

WARNINGS
CLOLAR® should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Suppression of bone marrow function should be anticipated. This is usually reversible and appears to be dose dependent. The use of CLOLAR® is likely to increase the risk of infection, including severe sepsis, as a result of bone marrow suppression. Administration of CLOLAR® results in a rapid reduction in lymphocyte count. For this reason, patients undergoing treatment with CLOLAR® should be evaluated and monitored for signs and symptoms of infection, including fever, as well as signs and symptoms of cytokine release (e.g., hypotension, tachycardia, hypertension, pulmonary oedema) that could develop into systemic inflammatory response syndrome (SIRS)/cytokine release syndrome, and organ failure. Physicians are encouraged to give close IV fluids throughout the five days of CLOLAR® treatment to reduce the effects of severe hypotension and other adverse events. Allergic reactions should be anticipated if high doses are given. This drug should be discontinued immediately in the event of clinically significant signs or symptoms of SIRS/cytokine release syndrome, either of which can cause death, and use of steroids, diuretics, and albumin considered. CLOLAR® may cause renal dysfunction even when the patient is stable, generally at a lower dose.

Severe bone marrow suppression, including neutropenia, anemia, and thrombocytopenia, has been observed in patients treated with CLOLAR®. At initiation of treatment, most patients in the clinical studies had a previous clinical performance as a manifestation of leukemia. Because of the pre-existing immunosuppressed condition of several of these patients, neutropenia can result from treatment with CLOLAR®, patients are at increased risk for severe opportunistic infections. Careful hematological monitoring during therapy is important, and hepatic and renal function should be assessed prior to and during treatment with CLOLAR® because of the CLOLAR®'s predominant renal excretion and because the liver is a target organ for CLOLAR® toxicity. The respiratory status and blood pressure should be closely monitored during infusion of CLOLAR®.

Hepatic and Renal Reactions
CLOLAR® has not been studied in patients with hepatic or renal dysfunction. Its use in such patients should be undertaken only with the greatest caution.

Pregnancy – Teratogenic Effects: Pregnancy Category D
CLOLAR® (clofarabine) may cause fetal harm when administered to pregnant women. It is not known whether clofarabine or its metabolites are excreted in human milk. Because of the potential for tumorogenicity shown for clofarabine in animal studies and the potential for carcinogenicity, it is advisable for patients to consider the advisability of using contraception during the treatment with CLOLAR®.

Information for Patients and Caregivers
Breastfeeding
Clofarabine is secreted in human milk. It is not known whether clofarabine or its metabolites are excreted in human milk. Because of the potential for carcinogenicity shown for clofarabine in animal studies and the potential for carcinogenicity, it is advisable for patients to consider the advisability of using contraception during the treatment with CLOLAR®.

Pregnancy/Nursing
All patients should be advised to use effective contraceptive measures to prevent pregnancy. Female patients should be advised to avoid breast-feeding during treatment with CLOLAR®.

Laboratory Tests
Complete blood counts and platelet counts should be obtained at regular intervals during CLOLAR® treatment, and frequently in patients who develop cytopenias. In addition, liver function should be monitored frequently during the 5 days of CLOLAR® administration.

Drug Interactions
Although no clinical drug-drug interaction studies have been conducted, it is not known whether CLOLAR® is a substrate, an inhibitor, or an inducer of cytochrome P450 isozyme or inducers are unlikely to affect the activity of CLOLAR®. The effect of chlorpromazine on the metabolism of cytochrome P450 substrates has not been studied.

Drug/Laboratory Tests Interactions
There are no known clinically significant interactions of CLOLAR® with other medications or laboratory tests. No formal drug/laboratory test interaction studies have been conducted with CLOLAR®.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
CLOLAR® did not induce clastogenic effects in the in vitro micronucleus test in hamster bone marrow cells derived from either males or females.

Mutagenesis
CLOLAR® administration caused clastogenic effects in the in vivo micronucleus test in hamster bone marrow cells derived from either males or females.

Fertility
CLOLAR® administration has not been studied for carcinogenic potential.

WARNINGS
Infection
Infections known to induce hepatic toxicity should also be avoided during the 5 days of CLOLAR® treatment. Physicians are encouraged to give continuous IV fluids throughout the five days of CLOLAR® treatment to reduce the effects of severe hypotension and other adverse events. Allergic reactions should be anticipated if high doses are given. This drug should be discontinued immediately in the event of clinically significant signs or symptoms of SIRS/cytokine release syndrome, either of which can cause death, and use of steroids, diuretics, and albumin considered. CLOLAR® may cause renal dysfunction even when the patient is stable, generally at a lower dose.

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Hepatic and Renal Reactions
CLOLAR® has not been studied in patients with hepatic or renal dysfunction. Its use in such patients should be undertaken only with the greatest caution.

Pregnancy
If pregnant women are to experience sterility or diarrhoea, they should be advised regarding appropriate means of contraception. Caution should be exercised in women who are pregnant or planning to become pregnant. CLOLAR® administration should be stopped if the patient develops evidence of pregnancy. Consideration should be given to alternative treatments. CLOLAR® administration can result in a nadir of bone marrow function at 10 to 14 days. The nadir should be anticipated if high doses are given. This drug should be discontinued immediately in the event of clinically significant signs or symptoms of SIRS/cytokine release syndrome, either of which can cause death, and use of steroids, diuretics, and albumin considered. CLOLAR® may cause renal dysfunction even when the patient is stable, generally at a lower dose.

Concomitant Medications
CLOLAR® is contraindicated primarily by the kidneys, drugs with known renal toxicity should be avoided during the 5 days of CLOLAR® administration, and other concomitant medications should be avoided. Patients taking medications known to affect blood pressure or cardiac function should be monitored during administration of CLOLAR®.

Pregnancy/Nursing
All patients should be advised to use effective contraceptive measures to prevent pregnancy. Female patients should be advised to avoid breast-feeding during treatment with CLOLAR®.

Laboratory Tests
Complete blood counts and platelet counts should be obtained at regular intervals during CLOLAR® treatment, and frequently in patients who develop cytopenias. In addition, liver function should be monitored frequently during the 5 days of CLOLAR® administration.

Drug Interactions
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CLOLAR® administration caused clastogenic effects in the in vivo micronucleus test in hamster bone marrow cells derived from either males or females.

Fertility
CLOLAR® administration has not been studied for carcinogenic potential.

DOSE AND ADMINISTRATION
Recommended Dose
CLOLAR® should be administered by intravenous injection or continuous intravenous infusion. The recomended dose is 40 mg/m2/day administered as a 52 mg/m2 daily x 5 every 28 days. More detailed information and guidelines for dose adjustments with higher or lower body surface area will be available. There are no known overdoses of CLOLAR®. The highest daily dose of CLOLAR® administered to patients or human volunteers in clinical trials at the recommended dose of 52 mg/m2 was 104 mg/m2 10/m05.

Patients with Severe Organ Dysfunction
Dose reduction to 80 mg/m2 should be considered if patients have hepatic or renal dysfunction. Its use in such patients should be undertaken only with the greatest caution.

Physicians are encouraged to give continuous IV fluids throughout the 5 days of CLOLAR® administration to reduce the effects of tachyphilia and other adverse events. The use of prophylactic drugs (e.g., 100 mg/kg hydrocortisone as Day 1 through 3) may be of benefit in preventing signs or symptoms of SIRS or capillary leak. Physicans should be aware of early manifestation of SIRS and should monitor carefully the use of prophylactic steroids and should provide appropriate support for the patient. The administration of the capillary leak syndrome is likely to increase the risk of infection (e.g., pneumonia). Physicians should be aware of signs or symptoms of SIRS or capillary leak (e.g., hypotension). The physician should immediately discontinue CLOLAR® administration and provide appropriate supportive measures. Close monitoring of renal and hepatic functions during the 5 days of CLOLAR® administration is advised. Severe increases in creatinine or bilirubin are not seen. Should CLOLAR® administration be stopped when there is no evidence of renal or liver dysfunction, then the patient should be re-evaluated before administering the drug.

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822-1016

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Infants under six months old, with abnormalities involving 11q23, appear to be at highest risk.

**Treatment of AML**

**Principles of Therapy**

The event-free survival rate in childhood AML has reached a plateau at 60%, despite aggressive intensification of therapy. Cytarabine and daunorubicin, in combination with either etoposide or thioguanine, will induce a complete remission in more than 90% of patients. Attempts to substitute idarubicin or mitoxantrone for daunorubicin, or increase the dose of cytarabine, have largely proven to be of comparable efficacy, and, occasionally, greater toxicity. Intensive post-remission therapies have been developed using multi-agent regimens cycled every four to six weeks. There have been no randomized, head-to-head comparisons of the different regimens, but none have succeeded in improving long-term, event-free survival beyond 60%. Most studies of allogeneic transplant in children with AML non-randomly assign patients with matched sibling donors to undergo transplant, and those without sibling donors to continue with conventional chemotherapy. Relapse-free survival is generally better in the patients who undergo transplantation, but overall survival is comparable due to transplant-related mortality.

**Acute Promyelocytic Leukemia**

Patients with acute promyelocytic leukemia (APML) do not do well with conventional AML therapy. Rather, regimens intensifying the anthracycline dose in induction and incorporating retinoic acid, mercaptopurine, and methotrexate into maintenance therapy have led to five-year survival rates exceeding 80% among children with APML.

**CML**

In children and adults, CML is characterized by the presence of the Philadelphia (Ph) chromosome. Until recently, standard therapy for CML in children and adults included hydroxyurea, interferon, and low-dose cytarabine. While clinical improvements in hematologic parameters were possible with these therapies, cytogenetic remission were infrequent. More recently, imatinib mesylate was developed as a specific inhibitor of the BCR-ABL (breakpoint cluster region–Abelson) tyrosine kinase. Results from recent clinical trials have rapidly established imatinib as the standard-of-care for CML, and cytogenetic remissions are now expected. Limited data are available on imatinib mesylate in children, but preliminary data are promising. Imatinib mesylate has dramatically changed therapy for CML, but it is still not a cure. The only proven curative strategy for children with CML is allogeneic stem cell transplantation (SCT). Survival after SCT for CML is reported to be 70–80% with a matched sibling donor and 40–60% when unrelated donors are used.

**Relapsed Leukemias and SCT**

**ALL**

Despite development of successful therapies in childhood leukemias, 20–25% of children with ALL and 50% of children with AML will relapse after chemotherapy treatment. In fact, more children are diagnosed with relapsed leukemia than Hodgkin’s disease (HD) and pediatric sarcomas. In most children with relapsed leukemia, long-term, event-free survival is less than 50%, even with SCT. Remission re-induction following relapse is relatively good, but overall survival remains poor, owing to a deficiency in effective therapies. The three-year, event-free survival for patients with a first remission less than 18 month is 4%; 18–30 months, 10%; and greater than 30 months, 41%. Most events occur within six months of relapse and fewer than half of the patients assigned to unrelated donor transplants actually made it to transplant in second remission. These results are striking and speak strongly to the need for additional therapies for ALL.

**AML**

As is the case with ALL, hematologic relapse remains the most common adverse event in patients with AML. About 30–40% of patients who achieve a remission will relapse, while 25% will have residual disease after intensive induction therapy. Remission re-induction rates for all patients with AML in first relapse ranges from 50–80% using multiagent chemotherapy. Overall survival following relapse is a dismal 30–40%.

---

**Table 6: European Group for the Immunological Characterization of Leukemias Scoring System**

<table>
<thead>
<tr>
<th>Points</th>
<th>B-Cell ALL</th>
<th>T Cell ALL</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>cyCD79</td>
<td>cyCD3 or memCD3</td>
<td>MPO</td>
</tr>
<tr>
<td>1</td>
<td>CD19</td>
<td>CD2</td>
<td>CD117</td>
</tr>
<tr>
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<td>CD5</td>
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<td></td>
<td>CD10</td>
<td>CD8</td>
<td>CD33</td>
</tr>
<tr>
<td>0.5</td>
<td>TdT</td>
<td>TdT</td>
<td>CD14</td>
</tr>
<tr>
<td></td>
<td>CD24</td>
<td>CD7</td>
<td>CD15</td>
</tr>
</tbody>
</table>

*cy = cytoplasmic, mem = membrane, TCR = T cell receptor, MPO = myeloperoxidase, TdT = terminal deoxynucleotidyl transferase*
New Agents

As high-dose chemotherapy with SCT is not enough for high-risk, relapsed, and refractory leukemias, new agents are clearly needed. One of the driving forces in the identification, rational synthesis, and development of new agents—many of which are the prototypes in entirely new classes of antineoplastics—is an improved understanding of the biological mechanisms involved in leukemogenesis.

Next Generation Cytotoxic Therapies

One strategy employed in new agent development is the encapsulation of proven agents in liposomes containing polyethylene glycol (PEG). Pegylated forms of doxorubicin, vincristine, all-trans retinoic acid (ATRA), and asparaginase are available. Pegylation increases the half-life, enhances tumor delivery of the compounds, decreases the vesicant effect of doxorubicin and vincristine, decreases the cardiac toxicity of doxorubicin, and reduces the number of intramuscular injections of asparaginase.

Cytarabine is a purine nucleoside analog with an excellent track record in pediatric leukemias, both AML and ALL. Fludarabine, cladribine, and clofarabine are nucleoside analogs developed more recently that are also effective in leukemias and have more favorable pharmacologic features than cytarabine. Based on a response rate of 31% (12% complete remission), clofarabine was recently approved for use in relapsed ALL in children. This is the first drug approved for such an indication in the US for more than two decades. Like cladribine and fludarabine, clofarabine may be used effectively in combination with cytarabine. As a potent inhibitor of ribonucleotide reductase, clofarabine may decrease intracellular deoxy-nucleotides, decreasing feedback inhibition of deoxycytidine (dCyd) kinase, and thus allowing for an increase in the accumulation of ara-CTP.

Nelarabine (compound 506U78) is a pro-drug of cytarabine. Early studies demonstrated that nelarabine is selectively toxic to lymphoblasts with an early T-cell phenotype. Initial Phase I and II trials conducted by the COG demonstrated activity with an overall response rate of 55% in first relapse, 25% in second relapse, and a few responses in third relapse. Unfortunately, there was significant neurotoxicity, including ataxia, confusion, and coma. The effect appears dose-dependent, and the incidence and severity decreased with dose de-escalation. Nelarabine is currently being tested by the COG in the backbone of an intensive BFM regimen for patients with newly diagnosed T-cell ALL.

Agents Targeting Specific Molecular Events

The remarkable success of imatinib mesylate in patients with CML demonstrated the potential of targeted therapies.

Tyrosine Kinase—results from recent clinical trials have rapidly established imatinib as the standard-of-care for CML. A recent phase III prospective trial of >1,000 patients conclusively demonstrated that imatinib is superior to interferon alpha (IFN-α) plus low-dose cytarabine in inducing cytogenetic disease remission and prolonging progression-free survival in adult patients with chronic-phase CML.

Dasatinib—(BMS-354825) is a potent inhibitor of Abl and Src (sarcoma) kinase activity. Imatinib resistance is frequently mediated by mutations in the Abl kinase domain. Unlike imatinib, dasatinib has affinity for all mutations of the Abl kinase domain. In a phase I trial of dasatinib in 36 imatinib-resistant (or intolerant) patients with CML in chronic phase, a complete hematologic response is reported in 86% of the patients, and a complete cytogenetic response by three months is reported in 28% of patients. These compounds will have affinity for other tyrosine kinases (e.g. Src, c-kit, platelet-derived growth factor receptor (PDGFR)) involved in the pathogenesis of all leukemias. However, it is not yet known what the clinical applications of these compounds will be when targeting non-Abl tyrosine kinases.

Thalidomide and Lenalidomide—thalidomide belongs to the class of compounds called imids. While the mechanism of action is largely unknown, imids do appear to inhibit cytokine production and angiogenesis, while enhancing stromal cell function. Thalidomide experienced a revival...
after demonstrating a 66% response rate in patients with multiple myeloma. Lenalidomide, is a synthetic compound with less neurotoxicity and teratogenicity. An 83% response rate is reported among patients with myelodysplastic syndrome (MDS) due to 5(q-).

Proteosome Inhibitors—proteosome inhibitors, like bortezomib, inhibit the breakdown of proteins through the ubiquitin-proteosome pathway. Inhibitors of cell cycle progression and the transcription factor NF-kB accumulate in cells treated with a bortezomib. In an open-label trial of patients with multiple myeloma, a 28% response rate is reported. In a subsequent phase III randomized trial comparing bortezomib to high-dose dexamethasone, a superior response rate is seen in the patients treated with bortezomib. A phase I trial has been completed by the COG, and phase II combinations are underway.

Arsenic Trioxide—as single agent therapy, arsenic trioxide may induce a complete remission in 90% of patients with APML. Success of this agent in APML has prompted multiple on-going studies in MDS, myeloma and AML.

Inhibitors of mTOR—the mammalian target of rapamycin (mTOR) is a serine-threonine kinase involved in the activation of Akt and downstream pathways. Rapamycin, an mTOR inhibitor, has demonstrated significant clinical responses in a few patients with relapsed and refractory AML.

Farnesyltransferase inhibitors—ras mutations are common in AML and MDS, and targeting Ras farnesylation is a novel approach currently under investigation. Tipifarnib (R115777) is a farnesyltransferase inhibitor with initial clinical responses in 10 out of 34 elderly patients with AML. Subsequent trials in patients with MDS, CML, and high risk AML were less encouraging. However, additional studies evaluating combinations with other agents are on-going.

Targeting Gene Expression

Histone acetylation/deacetylation and deoxyribonucleic acid (DNA) methylation are epigenetic phenomena that can effect gene expression. Chromatin remodeling agents targeting DNA methylation and histone acetylation are at present in clinical trials. Currently, there are two hypomethylating agents with activity in hematologic malignancies. 5-azacytidine is US Food and Drug Administration (FDA)-approved for adults with MDS and 5-aza-2’-deoxycytidine (decitibine) is currently in clinical trials in adults with MDS. Suberoylanilide hydroxamic acid (SAHA), high-dose valproate, and sodium butyrate are histone deacetylase inhibitors. Early investigations into these agents alone and in combination with hypomethylating agents are under way.

Monoclonal Antibodies

Rituximab is a chimeric monoclonal antibody that recognizes the CD20 antigen expressed on mature and immature B-cells. CD20 is expressed in some B-cell ALLs and B-cell non-Hodgkin’s lymphoma. Initial studies demonstrated that the addition of rituximab to the standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) backbone, enhanced survival among patients with B-cell lymphomas. Alemtuzumab is a monoclonal antibody that recognizes CD52 expressed on T-cells, some B-cells and NK cells. Epratuzumab is a humanized monoclonal antibody directed against CD22, an antigen expressed on mature and immature B-cells. In a phase I/II trial of epratuzumab in adult patients with lymphoma, there was a 33% response rate.

Gemtuzumab ozogamicin (GO) is a humanized monoclonal antibody, directed against the myeloid antigen CD33, conjugated with the cytotoxic agent calicheamicin. It is approved for use in adults with AML over age 60 years of age. In a phase I trial in pediatric patients GO demonstrated a 28% response rate. However, six of the 13 patients who later underwent SCT developed veno-occlusive disease (VOD). Following promising phase I results, the COG is currently evaluating the role of GO in the backbone of a daunorubicin, etoposide, and cytarabine induction. Humanized monoclonal antibodies conjugated to radioisotopes have also been developed.

Conclusions

Treatment of childhood leukemias is widely touted as a great success in oncology clinical trials, largely due to the continued incremental increases in long-term survival in children with ALL. Significant challenges still lie ahead as we define new strategies for treating AML and relapsed leukemias, as well as the myeloproliferative and myelodysplastic disorders. Application of risk-adapted therapy to patients with ALL and AML has allowed for continued improvement in long-term, event-free survival and a reduction in long-term side effects. What has been learned about leukemia biology, host pharmacogenetics, and environmental influences on leukemia development, has led to the development of effective strategies treatment and preventive strategies for childhood leukemias. There is still a significant amount of work to be done, but the future is bright.