Cognitive Effects of Cancer Therapies

Extraordinary progress has been made in treating childhood leukemia over the past 45 years. Using old and new therapies in ever more effective ways, doctors have been able to increase the five-year relative survival rate for acute lymphocytic leukemia (ALL)—the most common form of childhood leukemia—to 88.4% among patients under the age of five, and 86% among youngsters under the age of 15 in the US.

While leukemia remains the leading cause of death from cancer among children and young adults under the age of 20, the steady increase in survival is striking considering that a patient had only a 14% chance of living five years with the disease in 1960. In fact, pediatric cancer treatments have improved so markedly that experts estimate that one in 900 adults in 2010 will be a childhood cancer survivor, and most will live an average of 60 years from the time of their diagnosis.

Modern cancer therapies, like all medical interventions, have their share of complications and long-term side-effects; some of these involve the brain. In recent years, with an increasing number of pediatric cancer patients surviving into adolescence and young adulthood, experts have been diagnosing cognitive deficits caused by some of the same therapies that have saved so many. The problem may be becoming less severe as recent treatment protocols have diminished in toxicity. Nonetheless, the rate of cognitive impairment remains high.

As many as 40% of all pediatric ALL patients treated with chemotherapy alone will develop serious learning disabilities within two to three years following treatment. For children who receive cranial radiation, with or without chemotherapy, the percentage is 80–90%.

“The focus up until fairly recently has been on treating the cancers,” explained psychologist Daniel Armstrong, PhD, of the University of Miami, Florida, a noted expert in the cognitive effects of cancer treatments. “Now, we have a real awareness that there is life after cancer. We’re looking at the patient post-treatment, and that often means addressing such issues as serious lifelong cognitive deficits.”

Common late cognitive effects include:

- a marked slowing in thinking (processing) speed;
- attention problems, including daydreaming, ‘spacing out’ and a tendency to distract easily;
- memory difficulties, particularly with tasks that require visual cues, such as remembering numbers and new words;
- fine motor coordination problems;
- difficulty planning and organizing tasks and materials; and
- poor handwriting, reading comprehension, and mathematics skills, particularly in calculations.

Parents soon realize that little things become a major chore for a child with cancer-related cognitive disabilities. Simple homework becomes a six-hour ordeal every night, reading is difficult because of the energy expended to decode the phonetics of a word, making comprehension an afterthought. Handwriting may also be illegible. The emotional costs are also high. Children whose disabilities remain undiagnosed or under-treated sometimes have low self-esteem, which can lead to depression.

Those Vulnerable to Cancer and the Reasons for This

Among blood cancer patients, children with ALL and non-Hodgkin lymphoma seem to run a higher risk of developing later cognitive problems than patients who have battled other forms of blood cancers. Treatments that include high-dose methotrexate, given intravenously (IV) or injected directly into the spinal cord (intrathecal), cytarabine or cisplatin-type drugs increase the risk of learning disabilities later on. Children who receive radiation therapies, particularly to the head and neck, and total body irradiation in connection with a bone marrow
or peripheral stem cell transplant, are at a high risk of developing educational impairments.

According to the Children’s Oncology Group (COG), a National Cancer Institute (NCI)-supported clinical trials cooperative group devoted exclusively to childhood and adolescent cancer research, additional factors that may place children and teenagers at increased risk for difficulty in school include:

- diagnosis of cancer at a very young age;
- numerous or prolonged school absences;
- a history of learning difficulties before being diagnosed with cancer;
- cancer treatment that results in reduced energy levels;
- cancer treatment that affects hearing and vision; and
- cancer treatment that results in physical disabilities.

Young girls are more vulnerable to lingering cognitive problems than boys, although researchers do not fully understand why. However, scientists have a good understanding of why cancer therapies, while toxic to malignancies, can be so harmful to young brains and central nervous systems (CNSs). Radiation and chemotherapy can damage the tiny blood vessels that carry nutrition and oxygen to the brain, resulting in calcifications. “Blood doesn’t flow and oxygen doesn’t get there, and that could cause slow damage to the brain and its growth and development later on,” Dr Armstrong said.

Chemotherapy and radiation also interfere with the development of the myelin sheaths that protect nerve cells. Thin sheaths retard the brain’s ability to transmit information, slowing processing speed and affecting motor coordination. Finally, both chemotherapy and radiation disrupt the growth of neural network connections, inhibiting the smooth flow of electrical impulses in the brain, particularly around neural blockages and obstacles.

Detecting learning impairments can be difficult, but early testing and intervention can greatly improve a child’s chances of educational success. All children in high-risk groups should undergo a formal neuropsychological evaluation by a qualified pediatric psychologist at the time of entry into long-term follow-up care. Dr Armstrong recommended that children under the age of seven undergo a screening every 18 months, every 18 to 24 months for children aged seven to 12, and every three years as needed for children aged 12 to mid 20s.

Pediatricians and oncologists can play a role by informing parents during treatment that cancer and its therapies can cause cognitive problems. Armed with this knowledge, parents will not be so shocked if learning problems do emerge, and they have more time to advocate testing and remediation. Groups such as The Leukemia & Lymphoma Society (LLS), the COG and The Candlelighters® Childhood Cancer Foundation all offer suggestions to help healthcare professionals, teachers, and parents deal with the special needs of children returning to school after battling cancer.

Beginning in 2005 and running through to spring 2006, the LLS, with the support of The Lance Armstrong Foundation, is offering a special series of programs and booklets on this topic, offered online and through the LLS’s 64 chapters in the US.

Treatment Solutions

Treating cancer-related cognitive disabilities can include a combination of pharmaceutical, psychological, and educational approaches—the same strategies often used to treat non-cancer-related learning disabilities. On the medical front, recent NCI studies have shown that methylphenidate (Ritalin®) and other medications for attention deficit disorders may be effective in improving processing speed and memory in 60–70% of childhood cancer survivors with cognitive problems. If drug therapy is considered, doctors and parents need to...
discuss the risks and benefits of such treatments, and initial doses should be given at the cancer clinic so that doctors can monitor side effects. Antidepressants are useful in some cases, but also need to be administered under the close supervision of a physician.

For most children, the number one therapy is school. “School is the workplace, the learning place,” said Dr Armstrong. “Get them there as soon as possible, during and after treatment.” If tests confirm cognitive impairments, parents should contact their school immediately and request a personalized education plan for their child. There are several federal laws that protect children diagnosed with cancer and require schools to accommodate special-needs children. They include the Americans with Disabilities Act, the Rehabilitation Act 1973 (Section 504) and the Individuals with Disabilities Education Act. Once the specific learning disabilities are identified, educational strategies, ranging from the simple to the complex, may include:

- seating near the front of the class;
- assignment of a classroom aide;
- oral tests instead of written tests;
- reduced homework demands;
- limited handwriting requirements;
- extra help with mathematics, spelling, reading, and organizational skills;
- modification of test requirements, including minimizing or eliminating time limits and avoiding computerized answer sheets;
- large-print books;
- audio books;
- use of calculators in class and during tests;
- electronic organizers; and
- special computer software to facilitate learning, including voice-recognition programs that can scan printed material.

Optimism for the Future

While cognitive disabilities are generally lifelong conditions, most children with these deficits are capable of learning and can achieve full and happy lives, as long as they receive the proper support at school and in the home. “We are really looking at the future with hope,” Dr Armstrong said. “I know many childhood cancer survivors who have graduated from college and are leading productive lives. That kind of success takes a lot of work, a lot of education and a lot of knowledge on the part of the parent, the pediatric oncologist and the teacher. The key is to get the right services and to get them early.”

The Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society is the world’s largest voluntary health organization dedicated to funding blood cancer research, education and patient services. The Society’s mission is: “Cure leukemia, lymphoma, Hodgkin’s disease and myeloma, and improve the quality of life of patients and their families”. Since its founding in 1949, the Society has invested more than US$424 million for research specifically targeting blood cancers.

www.leukemia-lymphoma.org
In pediatric relapsed or refractory ALL respond with Clolar™

**Complete or Partial Response in Over 30% of Heavily Pretreated Patients**

In a phase 2 single arm, open label study in pediatric relapsed/refractory acute lymphoblastic leukemia (ALL) (n=49), over 30% achieved a complete or partial response.

All patients had disease that had relapsed after and/or was refractory to two or more prior therapies. Most patients, 46/49 (93.9%), had received 2 to 4 prior regimens and 15/49 (30.6%) of the patients had undergone at least 1 prior transplant.

6 of 15 patients who responded to treatment with Clolar were able to undergo post-treatment bone marrow transplantation, and response duration could not be determined. In the 9 responding patients who were not transplanted, response durations were: CR: 43, 50, 82, 93+, and 160+ days; CRp: 32 days; PR: 7, 16, and 21 days.

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, nausea, and diarrhea; hematologic effects, including anemia, leukopenia, thrombocytopenia, neutropenia, and febrile neutropenia; and infection. 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 immunocompromised 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 breast feeding while receiving treatment with clofarabine.

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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 of age with newly diagnosed acute lymphoblastic leukemia (ALL), including patients 1 to 10 years of age with favorable risk ALL, and patients 11 to 21 years of age with unfavorable risk ALL (including Philadelphia chromosome positive [Ph+], B-cell, and T-cell subtypes of ALL). It is also indicated for the treatment of pediatric patients 1 to 21 years of age with newly diagnosed acute myeloid leukemia (AML), including patients with intermediate risk and high risk disease, and patients with refractory disease. It is indicated for the treatment of pediatric patients 1 to 21 years of age with newly diagnosed high-risk relapsed or refractory acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML), including those with CNS involvement or central nervous system (CNS)-positive AML.

**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 does not appear to be dose-dependent. The use of CLOLAR™ is likely to increase the risk of infection, including opportunistic disease, as a result of bone marrow suppression. Administration of CLOLAR™ results in a rapid induction of profound myelosuppression. The patient undergoing treatment with CLOLAR™ should be evaluated and monitored for signs and symptoms of tumor lysis syndrome, as well as any other known adverse effects of cytotoxic therapy (e.g., tachycardia, tachypnea, hypotension, hypokalemia, pulmonary edema, or pleural effusion). Close monitoring and supportive care should be administered if hyperuricemia is suspected. CLOLAR™ should be discontinued immediately in the event of any serious or symptomatic SIRS or capillary leak syndromes, which are potentially life-threatening. It is important to monitor patients for evidence of SIRS during treatment with CLOLAR™ because of CLOLAR™'s predominate effects on lymphocytes and monocytes. Careful hematological monitoring during therapy is important, and hepatic and renal function studies should be conducted prior to and during treatment with CLOLAR™ because of CLOLAR™'s prominent effects on lymphocytes and monocytes. These abnormalities should be monitored closely during infusion of CLOLAR™.

**Hepatic and Renal Impairment**

CLOLAR™ is contraindicated in patients with hepatic or renal dysfunction, as its use in such patients should be undertaken only with the greatest caution.

**Pregnancy**

**Teratogenic Effects**

Pregnancy Category D

*See WARNINGS.*

**Nursing Mothers**

It is not known whether clofarabine or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in nursing women treated with clofarabine, it is not recommended that breast-feeding women use clofarabine. If the drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazards to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with clofarabine.

**PRECAUTIONS**

Information for Patients and Caregivers

Physicians are advised to discuss the following with patients to whom CLOLAR™ will be administered and patient caregivers, as well as other health care professionals who will be involved in the administration of CLOLAR™.

- **Symptoms of SIRS or Capillary Leak**
  - Fever
  - Rapid heart rate
  - Bradycardia
  - Hypotension
  - Distress
  - Hyperventilation
  - Pulmonary edema
  - Edema
  - Lethargy
  - Vomiting
  - Diarrhea
  - Hypokalemia
  - Hypotension
- **Signs of Cytokine Release**
  - Tachypnea
  - Tachycardia
  - Hypotension
  - Pulmonary edema
- **Signs of Tumor Lysis Syndrome**
  - Hypeension
  - Hypotension
  - Pulmonary edema
  - Edema
  - Lethargy
  - Vomiting
  - Diarrhea
  - Hypokalemia
  - Hypotension
  - Hypotension
- **Signs of Infection**
  - Fever
  - Rapid heart rate
  - Bradycardia
  - Hypotension
  - Distress
  - Hyperventilation
  - Pulmonary edema
  - Edema
  - Lethargy
  - Vomiting
  - Diarrhea
  - Hypokalemia
  - Hypotension
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  - Hypotension
  - Hypotension

**ADVERSE REACTIONS**

One hundred thirteen (113) pediatric patients with ALL (67) or AML (46) were exposed to CLOLAR™. Ninety-six (96) of the pediatric patients treated in clinical trials received the recommended dose of CLOLAR™ 52 mg/m2 daily x 5. The most common adverse effects after CLOLAR™ treatment were nausea, vomiting, diarrhea, and fever. Other common adverse events included grade 3 or 4 elevations in serum creatinine, aspartate aminotransferase (AST) occurred in 38% of patients and alanine aminotransferase (ALT) occurred in 10% of patients. The most common adverse events associated with CLOLAR™ treatment are listed in the following table. The table also includes the most common adverse events associated with CLOLAR™ treatment in the clinical studies. The relationship of these adverse events to CLOLAR™ treatment is unknown.

**CARDIAC ADVERSE EVENTS**

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 does not appear to be dose-dependent. The use of CLOLAR™ is likely to increase the risk of infection, including opportunistic disease, as a result of bone marrow suppression. Administration of CLOLAR™ results in a rapid induction of profound myelosuppression. The patient undergoing treatment with CLOLAR™ should be evaluated and monitored for signs and symptoms of tumor lysis syndrome, as well as any other known adverse effects of cytotoxic therapy (e.g., tachycardia, tachypnea, hypotension, hypokalemia, pulmonary edema, or pleural effusion). Close monitoring and supportive care should be administered if hyperuricemia is suspected. CLOLAR™ should be discontinued immediately in the event of any serious or symptomatic SIRS or capillary leak syndromes, which are potentially life-threatening. It is important to monitor patients for evidence of SIRS during treatment with CLOLAR™ because of CLOLAR™'s predominate effects on lymphocytes and monocytes. Careful hematological monitoring during therapy is important, and hepatic and renal function studies should be conducted prior to and during treatment with CLOLAR™ because of CLOLAR™'s prominent effects on lymphocytes and monocytes. These abnormalities should be monitored closely during infusion of CLOLAR™.