Cognitive Effects of Cancer Therapies

a report by
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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.

Miracle Treatments and Long-term Side Effects

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.

Early Intervention and Education—Keys to Success

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.

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.

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.

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.

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.

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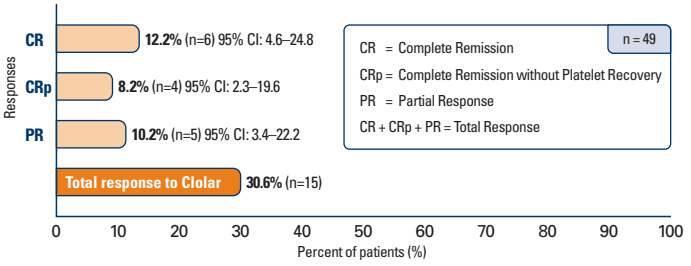
All patients had disease that had relapsed after and/or was refractory to two or more prior therapies. Most patients, 46/49 (93.8%), had received 2 to 4 prior regimens and 15/49 (30.6%) of the patients had undergone at least 1 prior transplant.

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.



Response rates were determined by an unblinded independent response review panel. Complete Remission (CR) defined as no circulating blasts or extramedullary disease, <5% bone marrow blasts, and recovery of peripheral blood counts (platelets >100 x 10^9/L and absolute neutrophil count [ANC] >1.0 x 10^9/L). Complete Remission in the Absence of Total Platelet Recovery (CRp) defined as meeting all criteria of CR except for recovery of platelet counts to >100 x 10^9/L. Partial Response (PR) defined as no circulating blasts, >5% and <25% bone marrow blasts, and appearance of normal progenitor cells.

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 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 breast feeding while receiving treatment with clofarabine.

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Brief Summary of Full Prescribing Information

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INDICATIONS AND USAGE

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.

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 peripheral leukemia cells. For this reason, patients undergoing treatment with CLOLAR™ should be evaluated and monitored for signs and symptoms of tumor lysis syndrome, as well as signs and symptoms of cytokine release (e.g., tachypnea, tachycardia, hypotension, pulmonary edema) that could develop into systemic inflammatory response syndrome (SIRS)/capillary leak syndrome, and organ dysfunction. Physicians are encouraged to give continuous IV fluids throughout the five days of CLOLAR™ administration to reduce the effects of tumor lysis and other adverse events. Allopurinol should be administered if hyperuricemia is expected. 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. CLOLAR™ can be re-instituted 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 hematological impairment as a manifestation of leukemia. 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. Careful hematological monitoring during therapy is important, and hepatic and renal function should be assessed prior to and during treatment with CLOLAR™ because of CLOLAR™'s predominantly 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 Impairment

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 a pregnant woman.

Clofarabine was teratogenic in rats and rabbits. Developmental toxicity (reduced fetal body weight and increased post-implantation loss) and increased incidences of malformations and variations (gross external, soft tissue, skeletal and retarded ossification) were observed in rats receiving 54 mg/m^2/day (approximately equivalent to the recommended clinical dose on a mg/m^2 basis), and in rabbits receiving 12 mg/m^2/day (approximately 23% of the recommended clinical dose on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women using clofarabine. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard 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 appropriate.

Dehydration/Hypotension

Patients receiving CLOLAR™ may experience vomiting and diarrhea; they should therefore be advised regarding appropriate measures to avoid dehydration. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, lightheadedness, fainting spells, or decreased urine output. CLOLAR™ administration should be stopped if the patient develops hypotension for any reason during the 5 days of administration. If hypotension is transient and resolves without pharmacological intervention, CLOLAR™ treatment can be re-instituted, generally at a lower dose.

Concomitant Medications

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. Patients taking medications known to affect blood pressure or cardiac function should be closely 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™ therapy, and more frequently in patients who develop cytopenias. In addition, liver and kidney function should be monitored frequently during the 5 days of CLOLAR™ administration.

Drug Interactions

Although no clinical drug-drug interaction studies have been conducted to date, on the basis of the *in vitro* studies, cytochrome p450 inhibitors and inducers are unlikely to affect the metabolism of clofarabine. The effect of clofarabine 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

Clofarabine has not been tested for carcinogenic potential.

Mutagenesis

Clofarabine showed clastogenic activity in the *in vitro* mammalian cell chromosome aberration assay (CHO cells) and in the *in vivo* rat micronucleus assay. It did not show evidence of mutagenic activity in the bacterial mutation assay (Ames test).

Impairment of Fertility

Studies in mice, rats, and dogs have demonstrated dose-related adverse effects on male reproductive organs. Seminiferous tubule and testicular degeneration and atrophy were reported in male mice receiving intraperitoneal (IP) doses of 3 mg/kg/day (9 mg/m^2/day, approximately 17% of the recommended clinical dose on a mg/m^2 basis). The testes of rats receiving 25 mg/kg/day (150 mg/m^2/day, approximately 3 times the recommended clinical dose on a mg/m^2 basis) in a 6-month IV study had bilateral degeneration of the seminiferous epithelium with retained spermatids and atrophy of interstitial cells. In a 6-month IV dog study, cell degeneration of the epididymis and degeneration of the seminiferous epithelium in the testes were observed in dogs receiving 0.375 mg/kg/day (7.5 mg/m^2/day, approximately 14% of the recommended clinical dose on a mg/m^2 basis). Ovarian atrophy or degeneration and uterine mucosal apoptosis were observed in female mice at 75 mg/kg/day (225 mg/m^2/day, approximately 4-fold of the recommended human dose on a mg/m^2 basis), the only dose administered to female mice. The effect on human fertility is unknown.

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 tumorigenicity shown for clofarabine in animal studies and the potential for serious adverse reactions, women treated with clofarabine should not nurse.

Other Special Population: Adults

Safety and efficacy have not been established in adults. One study was performed in highly refractory and/or relapsed adult patients with hematologic malignancies. The Phase 2 dose of CLOLAR™ was determined to be 40 mg/m^2/day administered as a 1- to 2-hour IVI daily x 5 every 28 days.

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/m^2 daily x 5.

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.

Table 1 lists adverse events by System Organ Class regardless of causality, including severe or life-threatening events (NCI CTC grade 3 or grade 4), reported in ≥10% of the 96 patients in the 52 mg/m^2/day dose group. More detailed information and follow-up of certain events is given below.

Table 1: Most Commonly Reported (≥10% Overall) Adverse Events by System Organ Class (N=96)

System Organ Class Adverse Event[1]	52mg/m^2 (N=96)					
	Total		Grade 3		Grade 4	
	N	%	n	%	n	%
Blood and Lymphatic System Disorders						
Febrile neutropenia	55	57	51	53	3	3
Neutropenia	10	10	3	3	7	7
Transfusion reaction	10	10	3	3	.	.
Cardiac Disorders						
Tachycardia NOS	33	34	6	6	.	.
Gastrointestinal Disorders						
Abdominal pain NOS	35	36	7	7	.	.
Constipation	20	21	.	.	.	.
Diarrhea NOS	51	53	10	10	.	.
Gingival bleeding	14	15	7	7	1	1
Nausea	72	75	14	15	1	1
Sore throat NOS	13	14	.	.	.	.
Vomiting NOS	80	83	8	8	1	1

Table 1: Most Commonly Reported (≥10% Overall) Adverse Events by System Organ Class (N=96) (Continued)

System Organ Class Adverse Event[1]	52mg/m^2 (N=96)					
	Total		Grade 3		Grade 4	
	N	%	n	%	n	%
General Disorders and Administration Site Conditions						
Edema NOS	19	20	1	1	2	2
Fatigue	35	36	3	3	1	1
Injection site pain	13	14	1	1	.	.
Lethargy	11	11	.	.	.	.
Mucosal inflammation NOS	17	18	3	3	.	.
Pain NOS	18	19	6	6	1	1
Pyrexia	39	41	15	16	.	.
Rigors	36	38	3	3	.	.
Hepato-Biliary Disorders						
Hepatomegaly	14	15	8	8	.	.
Jaundice NOS	14	15	2	2	.	.
Infections and Infestations						
Bacteremia	10	10	10	10	.	.
Cellulitis	11	11	9	9	.	.
Herpes simplex	11	11	6	6	.	.
Oral candidiasis	12	13	2	2	.	.
Pneumonia NOS	10	10	5	5	2	2
Sepsis NOS	14	15	7	7	7	7
Staphylococcal infection NOS	12	13	10	10	.	.
Investigations						
Weight decreased	10	10	1	1	.	.
Metabolism and Nutrition Disorders						
Anorexia	30	31	5	5	7	7
Appetite decreased NOS	11	11	.	.	.	.
Musculoskeletal, Connective Tissue and Bone Disorders						
Arthralgia	11	11	3	3	.	.
Back pain	12	13	3	3	.	.
Myalgia	13	14	.	.	.	.
Pain in limb	28	29	5	5	.	.
Nervous System Disorders						
Dizziness (except vertigo)	15	16	.	.	.	.
Headache NOS	44	46	4	4	.	.
Somnolence	10	10	1	1	.	.
Tremor NEC	10	10	.	.	.	.
Psychiatric Disorders						
Anxiety NEC	21	22	2	2	.	.
Depression NEC	11	11	1	1	.	.
Irritability	11	11	1	1	.	.
Renal and Urinary Disorders						
Hematuria	16	17	2	2	.	.
Respiratory, Thoracic and Mediastinal Disorders						
Cough	18	19	.	.	.	.
Dyspnea NOS	12	13	4	4	2	2
Epistaxis	30	31	14	15	.	.
Pleural effusion	10	10	3	3	2	2
Respiratory distress	13	14	6	6	5	5
Skin and Subcutaneous Tissue Disorders						
Contusion	11	11	1	1	.	.
Dermatitis NOS	39	41	7	7	.	.
Dry skin	10	10	1	1	.	.
Erythema NEC	17	18	.	.	.	.
Palmar-plantar erythrodysesthesia syndrome	12	13	4	4	.	.
Petechiae	28	29	7	7	.	.
Pruritus NOS	45	47	1	1	.	.
Vascular Disorders						
Flushing	17	18	.	.	.	.
Hypertension NOS	11	11	4	4	.	.
Hypotension NOS	28	29	12	13	7	7

1 Patients with more than one occurrence of the same preferred term are counted only once.

Grade 4 includes deaths (Grade 5).

Cardiovascular

The most frequently reported cardiac disorder was tachycardia (34%), which was, however, already present in 27.4% of patients at study entry. Most of the cardiac adverse events were reported in the first 2 cycles. Pericardial effusion was a frequent finding in these patients on post-treatment studies, [19/55 (35%)]. The effusion was almost always minimal to small and in no cases had hemodynamic significance.

Left ventricular systolic dysfunction (LVSD) was also noted. Fifteen out of fifty-five patients [15/55 (27%)] had some evidence of LVSD after study entry. In most cases where subsequent follow-up data were available, the LVSD appeared to be transient. The exact etiology for the LVSD is unclear because of previous therapy or serious concurrent illness.

Hepatic

Hepato-biliary toxicities were frequently observed in pediatric patients during treatment with CLOLAR™. Grade 3 or 4 elevated aspartate aminotransferase (AST) occurred in 38% of patients and grade 3 or 4 elevated alanine aminotransferase (ALT) occurred in 44% of patients. Grade 3 or 4 elevated bilirubin occurred in 15% of patients, with 2 cases of grade 4 hyperbilirubinemia resulting in treatment discontinuation.

For patients with follow-up data, elevations in AST and ALT were transient and typically of <2 weeks duration. The majority of AST and ALT elevations occurred within 1 week of CLOLAR™ administration and returned to baseline or ≤ grade 2 within several days. Although less common, elevations in bilirubin appeared to be more persistent. Where follow-up data are available, the median time to recovery from grade 3 and grade 4 elevations in bilirubin to ≤ grade 2 was 6 days.

Infection

At baseline, 47% of the patients had 1 or more concurrent infections. A total of 85% of patients experienced at least 1 infection after CLOLAR™ treatment, including fungal, viral and bacterial infections.

Renal

The most prevalent renal toxicity was elevated creatinine. Grade 3 or 4 elevated creatinine occurred in 6% of patients. Nephrotoxic medications, tumor lysis, and tumor lysis with hyperuricemia may contribute to renal toxicity.

Systemic Inflammatory Response Syndrome (SIRS)/ Capillary Leak Syndrome

Capillary leak syndrome or SIRS (signs and symptoms of cytokine release, e.g., tachypnea, tachycardia, hypotension, pulmonary edema) occurred in 4 pediatric patients overall (3 ALL, 1 AML). Several patients developed rapid onset of respiratory distress, hypotension, capillary leak (pleural and pericardial effusions), and multi-organ failure. Close monitoring for this syndrome and early intervention are recommended. The use of prophylactic steroids (e.g., 100 mg/m^2 hydrocortisone on Days 1 through 3) may be of benefit in preventing signs or symptoms of SIRS or capillary leak. Physicians should be alert to early indications of this syndrome and should immediately discontinue CLOLAR™ administration if they occur and provide appropriate supportive measures. After the patient is stabilized and organ function has returned to baseline, re-treatment with CLOLAR™ can be considered at a lower dose.

Overdosage

There were no known overdoses of CLOLAR™. The highest daily dose administered to a human to date (on a mg/m^2 basis) has been 70 mg/m^2/day x 5 days (2 pediatric ALL patients). The toxicities included in these 2 patients included grade 4 hyperbilirubinemia, grade 2 and 3 vomiting, and grade 3 maculopapular rash.

DOSAGE AND ADMINISTRATION

Recommended Dose

CLOLAR™ should be diluted per instructions below with 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion (IVI).

The recommended pediatric dose and schedule is 52 mg/m^2 administered by intravenous infusion (IVI) over 2 hours daily for 5 consecutive days. Treatment cycles are repeated following recovery or return to baseline organ function, approximately every 2 to 6 weeks. The dosage is based on the patient's body surface area (BSA), calculated using the actual height and weight before the start of each cycle. To prevent drug incompatibilities, no other medications should be administered through the same intravenous line.

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.

Physicians are encouraged to give continuous IV fluids throughout the 5 days of CLOLAR™ administration to reduce the effects of tumor lysis and other adverse events. The use of prophylactic steroids (e.g., 100 mg/m^2 hydrocortisone on Days 1 through 3) may be of benefit in preventing signs or symptoms of SIRS or capillary leak (e.g., hypotension). If patients show early 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 function during the 5 days of CLOLAR™ administration is advised. If substantial increases in creatinine or bilirubin are noted, physicians should immediately discontinue administration of CLOLAR™. CLOLAR™ should be re-instituted when the patient is stable and organ function has returned to baseline, possibly at a lower dose. If hyperuricemia is anticipated (tumor lysis), patients should prophylactically receive allopurinol.

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