

In conclusion, this review did not identify any unexpected safety concerns with the use of clofarabine in the pediatric population. We will continue to monitor routinely reports of adverse events in the pediatric population receiving clofarabine to increase our understanding of its effects in children.

AERS Search Results

AERS Search: All (U.S. and foreign) cases from December 28, 2004 (approval date) to August 14, 2005.

1. Raw counts of reports:

Age groups	All reports (US)	Serious (US)	Death (US)
All ages	47 (31)	45 (31)	21 (11)
Adults (≥ 17 yrs.)	31 (30)	(23)	(5)
Pediatrics (0-16 yrs.)	19 (12)	17 (11)	4 (3)

2. Raw counts of top 20 reported event PTs and labeling status of these events

All ages:

Hypotension (13), febrile neutropenia (12), sepsis (10), renal failure acute (7), diarrhea (6), renal failure (6), tachycardia (6), vomiting (6), bradycardia (5), erythema (5), edema peripheral (5), atrial fibrillation (4), bone marrow depression (4), general physical health deterioration (4), hypertension (4), pancytopenia (4), pulmonary edema (4), pyrexia (4), ventricular dysfunction (4) body temperature increase (3), cardiac arrest (3), cholelithiasis (3), depressed level of consciousness (3), dyspnea (3), enterococcal infection (3), fatigue (3), hemodialysis (3), hemoglobin decrease (3), hepatomegaly (3), hepatotoxicity (3), metabolic acidosis (3), multi-organ failure (3), nausea (3), edema (3), pain (3), pleural effusion (3), rash (3), somnolence (3), tachypnea (3)

Adults (>17 years):

Hypotension (11), neutropenia (10), sepsis (8), febrile neutropenia (7), renal failure acute (7), erythema (5), edema peripheral (5), renal failure (5), atrial fibrillation (4), bradycardia (4), general physical health deterioration (4), tachycardia (4), depressed level of consciousness (3), diarrhea (3), dyspnea (3), enterococcal infection (3), fatigue (3), hemodialysis (3), hypertension (3), edema (3), pain (3), pancytopenia (3), pyrexia (3), ventricular dysfunction (3)

Pediatrics (0-16 years):

Febrile neutropenia (5), vomiting (5), tachycardia (4), body temperature increased (3), bradycardia (3), cholelithiasis (3), diarrhea (3), hemoglobin decreased (3), hepatomegaly (3), hepatotoxicity (3), hypertension (3), pulmonary edema (3), ventricular dysfunction (3), atrial fibrillation (2), blood urea increased (2), bone marrow depression (2), cardiac arrest (2), hypotension (2), nausea (2), neutropenia (2), pleural effusion (2), tachypnea (2), tumor lysis syndrome (2)

Postmarketing Analysis of Pediatric Cases

Of the 19 reports, our search of the AERS database yielded 12 unique pediatric cases. Seven reports were not included for the following reasons: age (patient > 16 years old), report that was submitted pre-marketing, and duplicates (five reports). For the 12 cases, eight were from domestic sources and four were from foreign reporters. The children were between the ages of 1-15 years with a mean of 7 years and the gender ratio was 2:1 male-to-female. Five patients were hospitalized and four patients expired. All patients were treated with clofarabine for its approved indication of relapsed or refractory acute lymphoblastic leukemia, except for one patient who was treated for acute myelogenous leukemia. The characteristics of the cases are as follows:

Table 2. Characteristics of pediatric cases during the one-year period after receiving pediatric market exclusivity

Selected characteristic	N=12
Geographic location	
Foreign	4
Domestic	8
Age, years	
Range	1-15
Mean	7.2
Median	7
Gender	
Male	8
Female	4
Outcome	
Hospitalization [‡]	5 (1 died due to progressive disease later)
Anemia, thrombocytopenia	1
Hepatotoxicity	
Neutropenia	(3)
Death [‡]	4
Capillary leak syndrome (death due to progressive disease)	
Cardiac arrest	
Tumor lysis syndrome (death due to progressive disease)	
Fine motor tremors (but death due to med error s/p clofarabine tx)	
Life-threatening [‡]	1
Elevated creatinine	
Required intervention [‡]	1
Urticaria	
None	1
Hypotension	
Treatment indication	
Relapsed/refractory acute lymphocytic leukemia	11
Refractory acute myelogenous leukemia	1
Labeled adverse events (see Appendix 1)	
Neutropenia	3
Capillary leak syndrome	1
Anemia and thrombocytopenia	1
Elevated serum creatinine	1
Hepatotoxicity	1
Tumor lysis syndrome	1
Urticaria	1
Fine motor tremors	1
Hypotension	1
Unlabeled adverse event	
Cardiac arrest	1

[‡] Only one case of each adverse event occurred under each outcome (hospitalization, death, etc.), except for neutropenia, which had three cases.

The fatal cases are described below:

1. ISR #4726158-2, Foreign, Cardiac Arrest

A three year-old male patient with a history of refractory ALL started on clofarabine, consisting of 52 mg/m² daily for five days from April 13, 2005 to April 17, 2005 as part of a clinical trial study. On April 19, 2005, the patient experienced nausea, cyanosis and bradycardia. He was thought to have aspirated, so an attempt was made to suction his mouth and pharynx, which resulted in cardiac arrest and cessation of breathing. The patient had a cardiac arrest approximately (b) (6) hrs after his fifth dose of clofarabine. Cardiopulmonary resuscitation was initiated and performed for 45 minutes, but was unsuccessful and the patient expired on (b) (6)----- An autopsy of the chest and abdominal cavity was performed. An internal examination revealed a small amount of serous effusions in the body cavities (pericardial, pleural, and peritoneal). The heart was mildly dilated and the chest and abdominal cavities had multiple enlarged lymph nodes. On histological examination, the lungs were noted to be markedly congested with increased intraalveolar macrophages, consistent with the history of pulmonary edema. The thymus showed marked atrophy which was consistent with his severe illness. Kidney examination revealed probable early acute tubular necrosis with unknown etiology. The heart had individual myocardial fiber hypertrophy. Present throughout the heart, predominantly in the ventricles were individual necrotic myofiber. No evidence of inflammation reaction of the myocardial fiber was seen. The myocardial fiber changes were probably the cause of his ventricular dysfunction and arrhythmias. A possible relationship to the previous chemotherapy regimens which included cardiotoxic drugs (cytarabine) and to treatment with clofarabine was suspected. Prior to treatment with clofarabine, the patient had transient bradycardia during a CT scan requiring external cardiac massage on (b) (6)----- A vagal response was suggested as the cause. His electrocardiogram was normal, however, an echocardiogram post recovery showed mild left ventricular dilatation. A follow-up echocardiography on April 13, 2005 (prior to clofarabine therapy) revealed left ventricular dysfunction, mitral valve regurgitation, and tricuspid regurgitation.

2. ISR #4591388-X, Domestic, Tumor Lysis Syndrome (TLS)

A six year-old female with a history of ALL diagnosed in Spring 2001 started clofarabine treatment on January 26, 2005. The patient was previously treated with two oncology protocols (no specifics provided) with subsequent remissions and relapses. Following the second relapse, the patient had a bone marrow transplant in 2004 (exact date not given) and in June 2004, the patient experienced a third relapse in the bone marrow and central nervous system. Palliative treatment at this time included intrathecal methotrexate and cytarabine. On (b) (6)----- the patient relapsed again and was admitted to the hospital with a high temperature. She received gentamicin and started on etoposide 100 mg/m² twice weekly. On January 25 and 26, 2005, the patient received intravenous methotrexate. On January 26, 2005, the patient had a WBC of 1200/mm³, a platelet count of 37,000 plts/mm³ (onset date not provided), and a peripheral blast count of 56% and was started on clofarabine treatment (unknown dose). The patient died on (b) (6)----- Cause of death was unknown at the time of this report, but was thought to be related to TLS resulting in multi-organ system failure with hepatorenal syndrome and abdominal compartment syndrome.

3. ISR #4211771-9, Domestic, Capillary Leak Syndrome

A seven year-old female was initially diagnosed with stage I (left inguinal mass) precursor-B lymphoblastic lymphoma in January 2001 and was treated according to COG protocol A5971. Therapy was completed in February 2003. In March 2004, she relapsed with precursor-B lymphoblastic leukemia. She was re-induced with intense chemotherapy per COG protocol AALL01P2. Her course was complicated with disseminated fungal infection (sinuses, brain, and lung), recurrent varicella zoster virus, and several episodes of bacteremia. She underwent a 9/10 matching bone marrow transplant on (b) (6) ----- Her post-transplant course was complicated with *Clostridia difficile* infections, several episodes of bacteremia, and grade I abdominal graft-versus-host disease (GVHD). In January 2005, approximately five months post-transplant, she presented with a four-week history of small pericardial effusion, bilateral knee effusions, and a two-week history of bone pain. A complete blood count revealed a white blood cell count of 8100/mm³ with 30% blasts. She was hospitalized for further management. On January 22, 2005, she received one dose (first of five-day course) of clofarabine at 40 mg/m² (40 mg) intravenously over one hour at 2:15 P.M. At 6:00 P.M., she developed increased difficulty with breathing. A chest radiograph showed pulmonary edema, but no effusion. She received two doses of furosemide with no improvement. Over the next several hours, her blood pressure became tenuous. She was transferred to the intensive care unit for intubation and respiratory support as well as blood pressure support. She rapidly developed anasarca. The findings of pulmonary edema, shock, anasarca, and subsequent renal failure were felt to be consistent with capillary leak syndrome, a known complication of clofarabine. The patient had a prolonged stay in the intensive care unit and was eventually transferred to the floor on February 2, 2005. She did not receive any additional doses of clofarabine. When she stabilized, she received maintenance type therapy with prednisone and doxorubicin. She succumbed to her disease and expired on (b) (6) ----- .

4. ISR #4691401-5, Domestic, Fine Motor Tremors

A 13 year-old female diagnosed with acute lymphoblastic leukemia in December 1999 four consecutive clofarabine infusions (dose not specified) from January 16, 2005 through January 19, 2005. Fourteen days after her last clofarabine infusion, she experienced fine motor tremors. These were of the same intensity as those experienced prior to clofarabine treatment and resolved spontaneously within 48 hours. The reporter assessed that the fine motor tremors were not associated with clofarabine. Subsequently, the patient died on (b) (6) ----- due to a cardiac arrest related to a medical error which involved a non-leukemic medication. The patient also experienced fine motor tremors with other prior chemotherapy.

DISCUSSION

The AERS database was searched for reports of adverse events occurring with clofarabine use in pediatric patients. Pediatric cases are usually reviewed for a one-year period following the approval of pediatric exclusivity, but our review window is shorter because clofarabine received marketing approval on December 14, 2004, although pediatric exclusivity was granted on July 14, 2005. Thus, the review time period is from December 14, 2004 to August

15, 2005. We also compared the profile of adverse events for pediatric patients to that of the adult population. Nineteen (raw count) of the 50 cases received in the pediatric exclusivity period were reported in pediatric patients. The significant number of pediatric cases can be explained by the fact that clofarabine was approved to treat patients 1 to 21 years of age with relapsed or refractory ALL after at least two prior regimens.

Manual review of the reports revealed 12 unduplicated pediatric cases reported to FDA during the pediatric exclusivity period. Except for one, all patients in these cases experienced adverse events which are labeled.

Comparison of pediatric adverse events and adult adverse events

Because clofarabine is primarily indicated for the treatment of relapsed and refractory ALL in the pediatric population, comparing the adverse event profile to the adult to the pediatrics may be limited in its utility. Nonetheless, profile evaluation of the top 20 pediatric adverse events and adult adverse events were quite similar. Additionally, given that clofarabine is indicated for second-line ALL treatment, some of the adverse events may be attributable to disease state or other concomitant medications. The adverse events are considered expected per the product label.

Labeled events

The labeled adverse events (see Appendix 1) are listed in Table 1 and include capillary leak syndrome, anemia and thrombocytopenia, hypotension, hepatotoxicity, TLS, urticaria, and fine motor tremors. Five patients were hospitalized for adverse events consisting of anemia and thrombocytopenia, hepatotoxicity, and neutropenia (three patients), and one patient expired secondary to tumor lysis syndrome. All events were observed in the sponsor's pre-marketing safety database consisting of 133 pediatric patients with ALL or AML, as described in the "Adverse Reactions" section (see Appendix 1). Our case series shows that neutropenia was the most frequently reported labeled adverse event and this event was observed in 10% of patients in the Sponsor's safety database.

Unlabeled events

The case series included one case of an unlabeled event, specifically cardiac arrest and fine motor tremors. Causality is difficult to ascertain in the case of cardiac arrest as it appears to be confounded given the patient's pre-existing cardiac problems. One week prior to clofarabine, the patient had an episode of transient bradycardia requiring external cardiac massage and his baseline echocardiogram prior to clofarabine showed cardiac dysfunction.

Fatal outcomes

As shown in Table 1 and described under the "Results" section, four deaths in the pediatric population were associated with clofarabine use. One fatal outcome (ISR #4591388-X) was associated with a labeled event, namely TLS. In the three other cases, the deaths were caused by disease progression, medical error unrelated to clofarabine, and cardiac arrest confounded

by underlying cardiac history. Tumor lysis syndrome is a potentially fatal complication secondary to tumor cell death and cases of death have occurred.¹

CONCLUSION

In conclusion, this review did not identify any unexpected safety concerns with the use of clofarabine in pediatric patients. We will continue to monitor routinely reports of adverse events in the pediatric population receiving clofarabine to increase our understanding of its effects in children.

Appendix 1

Clofarabine Product Label

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 (eg, 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™.

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 × 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 2 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/m²/day dose group. More detailed information and follow-up of certain events is given below.

Table 2: Most Commonly Reported ($\geq 10\%$ Overall) Adverse Events by System Organ Class (N=96)						
System Organ Class Adverse Event¹	52 mg/m² (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
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	.	.

Table 2: Most Commonly Reported ($\geq 10\%$ Overall) Adverse Events by System Organ Class (N=96) (continued)						
System Organ Class Adverse Event¹	52 mg/m² (N=96)					
	Total		Grade 3		Grade 4	
	n	%	n	%	n	%
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 (exc 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 AST occurred in 38% of patients and grade 3 or 4 elevated 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 (eg, 100 mg/m² 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.

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¹ Arrambide K, Toto RD. Tumor lysis syndrome. Semin Nephrol. 1992;13:273-80.

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/s/

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