

# DIS News

College of Health Professions and Biomedical Sciences  
Drug Information Service

## Clofarabine For Pediatric Refractory Relapsing Acute Lymphoblastic Leukemia

In children under the age of 15, the most common malignancy is acute lymphoblastic leukemia (ALL). Of the 3500 cases diagnosed annually in the US, 2400 occur in children. The five year survival rate for pediatric ALL is approximately 80%.<sup>1</sup> While pediatric ALL has relatively good survival rates, relapsed/refractory pediatric ALL has a median survival time of less than one year.<sup>2</sup>

The goal of therapy in ALL is achievement of complete hematologic remission, defined as less than 5% blasts in the marrow. Treatment consists of remission induction followed by consolidation, then maintenance. Current regimens produce induction remissions in greater than 95% of children.<sup>1</sup> Since there is no standard therapy for relapsed/refractory ALL, patients are often retreated with standard induction therapy. If a favorable response is achieved, then an allogeneic stem cell transplant may be considered. Typically, remission is shorter with each re-treatment.

On December 29, 2004, the U.S. Food and Drug Administration granted accelerated marketing approval for Clolar™ (clofarabine) manufactured by Genzyme Corporation. It is indicated for the treatment of patients one to 21 years old with

relapsed or refractory ALL who have received at least two prior regimens. Clofarabine is a new hybrid purine nucleoside analog that inhibits synthesis of DNA.<sup>3,5</sup> Like other purine nucleoside analogs, clofarabine is a prodrug and must be converted intracellularly to the active triphosphate form by the converting enzyme deoxycytidine kinase (dCyd). In contrast to other purine nucleoside analogs, clofarabine has a very high affinity for dCyd kinase and a long intracellular half-life (> 24hrs).<sup>3,4</sup>

FDA approval was based on the induction of complete responses in a single-arm, open-label, non-randomized trial that has not been published.<sup>5</sup> Randomized trials demonstrating increased survival or other clinical benefit have not been conducted in refractory or relapsed ALL.

In the single-arm study, 49 patients with relapsed/refractory ALL received 52 mg/m<sup>2</sup> daily for five days.<sup>5</sup> A median of two cycles was administered (range 1-8 cycles). Treatment cycles were spaced at approximately two to six week intervals. Most of the patients (93.8%) had previously undergone two to four treatment regimens. The primary endpoints were complete remission (CR) and complete remission without recovery of platelet counts (CRp). Fifteen (30.6%) patients had at least a partial response to clofarabine.

Six patients (12.2%; 95% CI, 4.6-24.8) achieved a CR, and four patients (8.2%; 95% CI, 2.3-19.6) achieved a CRp. Six of the responding patients had stem cell transplants after treatment. For patients experiencing CR, the response lasted from 43 to greater than 160 days.<sup>5</sup>

The most common side effects observed included GI toxicities and transient LFT elevation. Less common but serious side effects include tumor lysis syndrome and systemic inflammatory response syndrome (SIRS) or capillary leak syndrome.<sup>5</sup>

An unmet medical need exists for pediatric patients who relapse or are refractory to initial ALL therapy. Due to the relatively small patient population, very few new compounds have been tested to meet this need. Clofarabine is the first new leukemia treatment approved specifically for children in more than a decade. Clofarabine (Clolar™) is available at an average wholesale cost of \$2700 for a 20 mg/20 mL vial.<sup>6</sup>

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### Inside this issue:

|                                 |   |
|---------------------------------|---|
| The Elidel® and Protopic® Scare | 2 |
| References                      | 4 |



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*We welcome any comments or suggestions for future newsletter topics.*

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# The Elidel® and Protopic® Scare

On March 10, 2005, the FDA issued a public health advisory warning patients and healthcare providers about a potential risk of cancer with the use of Elidel® (pimecrolimus) cream and Protopic® (tacrolimus) ointment.<sup>1</sup> Pimecrolimus and tacrolimus are topical calcineurin inhibitors used for the treatment of moderate to severe atopic dermatitis (AD) in patients two years of age and older who are unresponsive or cannot tolerate other treatments.<sup>1-4</sup> The advisory stems from post marketing case reports of lymphoma and skin cancer in humans as well as increased cancer rates in animal studies. Furthermore, the mechanism of action of these medications may theoretically impair local immunosurveillance, allowing proliferation of cancerous cells.<sup>1,5,6</sup>

Following the actions of the FDA, Novartis issued a statement to healthcare providers with additional information on pimecrolimus cream. The animal studies showed lymphoma development occurred following high oral doses of an experimental form of pimecrolimus, not in using the topical form currently on the market (doses were 17 times higher than the maximum recommended dose). Furthermore, the drug levels found in these animals could not be achieved using the topical cream, and clinical studies in humans show that blood levels of pimecrolimus cream are too low to be measured.<sup>7</sup>

After reviewing the data presented by the FDA, the National Eczema Association for Science and Education (NEASE) released the following statement:

- The incidence of lymphoma and skin cancers in patients treated with these medications appears to be less than expected. Both companies that produce these drugs have initiated long term registries of patients on these medications and some patients have been followed for almost five years already.
- The types of lymphoma reported in patients treated with these medications are not the types that arise in immunocompromised hosts as might be expected if these medications allowed cancers to form.
- Little evidence supports the contention that patients treated with these medications become immunocompromised.
- In general the blood levels observed in patients treated with these medications within the approved care standards are very low and transient.

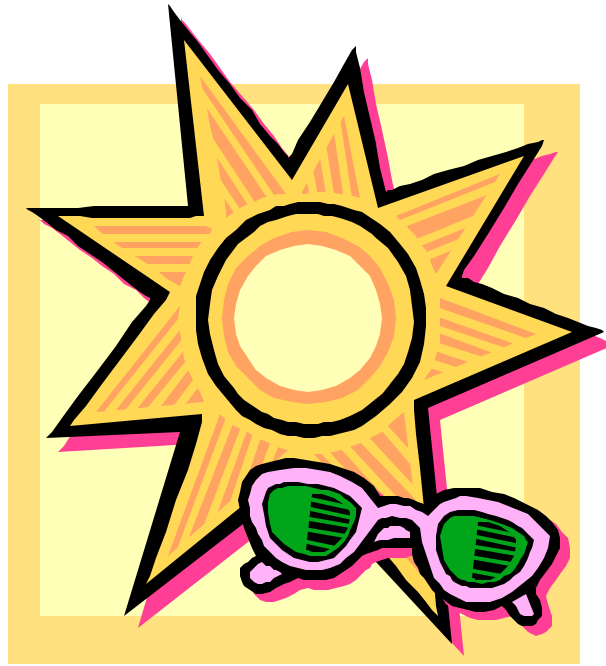
*Excerpt from NEASE Statement<sup>8</sup>*

The NEASE believes that these medications are safe when prescribed and used in the approved manner and with protection from the sun. Furthermore, they plan on conducting long-term studies on the safety of calcineurin inhibitors.<sup>8</sup>

Neither medication is approved for use in children less than two years old; however, a two year follow-up study was recently published on the safety and efficacy of pimecrolimus cream in infants 3-23 months old.<sup>9</sup> This was an extension to a previous randomized, double-blind, one-year study where subjects who received pimecrolimus had the option to continue therapy for a second year. In the first year, patients in the pimecrolimus group experienced significantly less flares compared to the control group ( $p < 0.001$ ), and there was no difference in adverse effects.<sup>10</sup> For an additional year, 76 patients continued to receive pimecrolimus cream, and 15 patients who previously received the control vehicle were converted to pimecrolimus cream ( $n=91$ ).<sup>9</sup> Participants were instructed to apply pimecrolimus twice daily at the first sign of AD to prevent a severe flare. Topical corticosteroids were allowed for flares not controlled with pimecrolimus. Eighty-one subjects completed one year of treatment, with most patients discontinuing because of withdrawal of consent. Adverse events reported included disorders common in early childhood such as nasopharyngitis, pyrexia, cough, diarrhea, ear infection, bronchitis, and gastroenteritis. One case of impetigo and one case of eczema were suspected to be associated with the medication; however, overall tolerability was good. Patients who received pimecrolimus for two years showed a decreased incidence of flares, with no flares reported in 77.6% in the first year and 85.5% after the extension. By the end of the second year, 71.4% of patients were clear or almost clear of AD symptoms compared to 36.3% in the first year. The authors concluded that pimecrolimus cream is safe and effective in infants and young children for long-term control of AD. Furthermore, early intervention may help modify disease progression and limit the use of topical corticosteroids.<sup>9</sup>

All medications pose a risk of adverse reactions, and the benefits of treatment need to be weighed against the risks. Elidel® and Protopic® are no exception. The available literature indicates there may be an increased risk of cancer in animal models; however, the association is inconclusive in human studies. Until further data become available, topical pimecrolimus and tacrolimus should be used according to the approved labeling and monitored closely.

*By Genine Thormahlen, Pharm. D.*



**Enjoy Your Summer**

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## References

### Clolar™

1. Day SD, Henry DW. Acute leukemia. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy. A pathophysiologic approach*. 5<sup>th</sup> ed. New York (NY): McGraw Hill;2002. p. 2373-2395.
2. Weitman S, Ochoa S, Sullivan J, Shuster J, Winick N, Pratt C, et al. Pediatric phase II cancer chemotherapy trials: a pediatric oncology group study. *J Pediatr Hematol Oncol* 1997; 19(3):187-191.
3. Parker WB, Shaddix SC, Rose LM, Shewach DS, Hertel LW, Secrist JA 3<sup>rd</sup>, et al. Comparison of the mechanism of cytotoxicity of 2-chloro-9-(2-deoxy-2-fluoro-beta-D arabinofuranosyl)adenine, 2-chloro-9-(2-deoxy-2-fluoro- beta-D-ribofuranosyl)adenine, and 2-chloro-9-(2-deoxy-2,2-difluoro- beta-D-ribofuranosyl)adenine in CEM cells. *Mol Pharmacol* 1999; 55(3):515-520.
4. Gandhi V, Kantarjain H, Faderl S, Bonate P, Du M, Ayres M, et al. Pharmacokinetics and pharmacodynamics of plasma clofarabine and cellular clofarabine triphosphate in patients with acute leukemias. *Clin Cancer Res* 2003; 9:6335-6342.
5. Genzyme Oncology. Clolar™ package insert. Cambridge ,MA:

2004 December.

6. P&T Quik® Reports. Thomson Micromedex, Greenwood Village, Colorado (Accessed April 2, 2005).

### Elidel® and Protopic®

1. FDA Public Health Advisory. Elidel (pimecrolimus) cream and Protopic (tacrolimus) ointment (March 10, 2005). FDA web site. Available at: [http://www.fda.gov/cder/drug/advisory/elidel\\_protopic.htm](http://www.fda.gov/cder/drug/advisory/elidel_protopic.htm). Accessed March 29, 2005.
2. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, Colorado (Accessed on April 21, 2005).
3. Novartis. Elidel® prescribing information. East Hanover NJ: 2004 July.
4. Fujisawa Healthcare. Protopic® prescribing information. Deerfield IL: 2002 August.
5. Alert for healthcare professionals. Pimecrolimus (marketed as Elidel) (March 2005). FDA web site. Available at: <http://www.fda.gov/cder/drug/InfoSheets/HCP/ElidelHCP.pdf>. Accessed March 29, 2005.
6. Alert for healthcare professionals. Tacrolimus (marketed as Protopic) (March 2005). FDA web site. Available at: <http://www.fda.gov/cder/drug/InfoSheets/HCP/ProtopicHCP.pdf>. Accessed March 29, 2005.
7. Hoover K, Novartis Pharmaceuti-

als. Personal communication. March 2005.

8. The National Eczema Association's statement concerning the use of Protopic and Elidel (topical calcineurin inhibitors) (n.d). National Eczema Association web site. Available at: <http://www.nationaleczema.org/NEASEStatementToPatients.Mar2005%20FINAL.doc>. Accessed April 21, 2005.
9. Papp KA, Werfel T, Folster-Holst R, Ortonne JP, Potter PC, de Prost Y, et al. Long-term control of atopic dermatitis with pimecrolimus cream 1% in infants and young children: a two-year study. *J Am Acad Dermatol* 2005; 52:240-6.
10. Kapp A, Papp K, Bingham A, Folster-Holst R, Ortonne JP, Potter PC. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. *J Allergy Clin Immunol* 2002; 110(2):277-284.



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