Fenretinide (N-4-hydroxyphenyl-retinamide, or 4-HPR) is a semisynthetic retinoid that was initially developed as a low-dose chemopreventative agent.[1-3] Unlike other naturally occurring retinoids such as all-trans, 13-cis, and 9-cis retinoic acids, fenretinide does not induce systemic catabolism that interferes with the maintenance of effective plasma levels during long-term use. This characteristic, combined with the agent’s low toxicity and its ability to block aspects of carcinogenesis, provided the rationale for the development of fenretinide in lower doses as a chemoprevention agent for breast, prostate, and bladder cancer.

**Apoptotic Effects**

More recently, fenretinide has been shown to exert antiproliferative effects on malignant cells that appear to be independent of the cytodifferentiation response common with other retinoids. Two distinct responses to fenretinide were identified in F9 embryonal carcinoma cells.[4] A rapid induction of cell death occurred at 10 µM fenretinide in both wild-type and retinoid-receptor null mutants, and a slower induction of differentiation occurred at 1 µM in wild-type cells only. In myeloid leukemia and lymphoma cell lines, fenretinide concentrations of at least 3 µM were associated with the induction of apoptosis, whereas concentrations lower than 1 µM resulted in cytostatic effects.[5] Similar observations of apoptosis associated with high concentrations of fenretinide in vitro have been reported in various leukemia and lymphoid cells,[6-8] as well as in neuroblastoma,[9-11] small cell[12] and non-small- cell lung cancer,[13] prostate cancer,[14-16] cervical carcinoma,[17,18],
bladder cancer,[19] and head and neck squamous carcinoma.[20,21]

**Mechanism of Action**

The mechanism of action of fenretinide-induced apoptosis is not fully understood. It is hypothesized that this compound can act independently of the nuclear retinoid receptor pathway.[5] Evidence using antioxidants and oxygen radical scavengers in myeloid (HL-60) cells and cervical carcinoma (C33A) cells points to the initiation of apoptosis by fenretinide-induced generation of reactive oxygen species.[22,23] Further data from C33A cells indicate that the molecular site of this fenretinide-induced generation of reactive oxygen species is between the complex II and complex III enzymes of the mitochondrial respiratory chain, presumably coenzyme Q.[24] It has also been reported that fenretinide-induced apoptosis is linked with activation of the stress-activated protein kinase (c-Jun N-terminal kinase, or JNK) in LNCaP prostate carcinoma cells, independent of reactive oxygen species generation and caspase activation.[25] Another reported mechanism of fenretinide cytotoxicity links increased de novo synthesis of ceramide in neuroblastoma cells with cell death in a p53- and caspase-independent manner.[26-28] Evidence from colon carcinoma cells suggests that fenretinide inhibits cell growth by inhibiting the expression of the COX-2 gene leading to diminished prostaglandin synthesis.[29] And finally, other studies suggest that in certain cell types, fenretinide may act by selective activation of nuclear retinoid receptors.[30-32]

**Phase I Clinical Experience**

In order to determine whether it would be possible to achieve in patients' plasma the same concentrations of fenretinide that were shown to induce apoptosis in vitro (≥ 3 mM), the National Cancer Institute/Cancer Therapy and Evaluation Program (NCI/CTEP) sponsored two phase I studies of high dose fenretinide in adults and children. Both of these trials employed a twice-daily (bid) oral regimen for 7 days, followed by a 2-week rest before repeating the cycle. To increase drug absorption, patients were encouraged to take each dose with 8 oz of whole milk and with morning and evening meals. Doses for adults ranged from 500 to 3,400 mg/m²/d, and pediatric doses ranged from 350 to 3,300 mg/m²/d. In the adult trial, three-times-daily (bid) dosing was explored as a means of increasing fenretinide plasma levels and of improving the tolerability of ingesting the large number of capsules.

Major toxicities among the 31 adults treated were grade 1/2 dry skin and grade 1/2 nyctalopia (night blindness), which were reversible on cessation of drug treatment.[33] Other toxicities were nausea, vomiting, diarrhea (grade 1/2), abdominal cramping (grade 1) and a single case of grade 3 hepatic dysfunction (at a dose level of 4,800 mg/m²) that first manifested 2 weeks after completion of treatment. Failure to reach toxicity was associated with maximum achievable plasma levels of fenretinide that occurred at 900 mg/m² bid. This is believed to be due to saturable absorption or accumulation of the drug in the gut wall (and possibly in other organs), but not to metabolism to the inactive metabolite 4-methoxyphenyl retinamide (4-MPR). Because similar systemic exposures were observed after bid and tid dosing, and the maximum achievable plasma concentration was reached at the 900 mg/m² bid dose, an adult dose of 900 mg/m² bid is recommended for phase II trials.

Toxicity was more severe among the 50 children who received fenretinide, with individual cases of increased intracranial pressure (grade 4) that appeared to be idiosyncratic, occurring at doses of 600, 800, and 3,300 mg/m²/d. Also reported were hypoalbuminemia and hypophosphatemia (both grade 3) at a dose of 1,860 mg/m²/d, and elevated transaminases (grade 3) at 3,300 mg/m²/d.

**Dosage Levels**

Plasma levels of fenretinide were in the range associated with induction of apoptosis in vitro, but lower than expected for the dose given, suggesting saturable absorption. Adults at the 2,400 and 3,400 mg/m²/d dose levels achieved fenretinide plasma levels of 9 to 10 µM, and children achieved plasma levels of 3 to 8 µM at the 600 mg/m² dose level. In both children and adults, there was an increase in the area under the time-concentration curve (AUC) on days 6 to 8 as compared to day 1 of treatment. By day 7 of treatment in children, plasma retinol levels declined to less than 10% of pretreatment levels, but rebounded quickly following discontinuation of the drug. Two adult patients achieved a less than partial response: one with breast cancer through 12 cycles, and one with renal cell cancer through 9 cycles. Notably, 1 child with bone marrow involvement by neuroblastoma achieved a complete response, while 11 additional children with neuroblastoma had stable disease.
Although the maximum tolerated dose of fenretinide has not yet been reached in the pediatric phase I study, it is likely that the recommended phase II dose will be approximately 2,500 mg/m²/d.

**Phase II**

**Title:** Phase II Trial of Fenretinide in Patients With Recurrent Small-Cell Lung Cancer  
**Protocol Number:** CCUM-9940, NCI-T99-0112  
**Participating Institutions:** University of Michigan Medical Center, Wayne State University  
**Protocol Status:** Active  
**Contact:** Gregory P. Kalemkerian, MD, (734) 936-5281  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Title:** Phase II Study of Fenretinide in Patients With Recurrent Small-Cell Lung Cancer  
**Protocol Number:** MDA-ID-95236, NCI-G99-1621  
**Participating Institutions:** M. D. Anderson Cancer Center, Baylor University Medical Center  
**Protocol Status:** Active  
**Contact:** H. Barton Grossman, MD, (713) 792-3250  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Title:** Phase II Study of Fenretinide in Patients With Recurrent Malignant Glioma  
**Protocol Number:** NABTC-9905, UCLA-0006094  
**Participating Institution:** North American Brain Tumor Consortium  
**Protocol Status:** Active  
**Contact:** Vinay K. Puduvalli, MD, (713) 794-1286 or (713) 745-0187; for a complete listing of study contacts, click here  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Title:** Phase II Study of Fenretinide in Patients With Advanced Renal Cell Carcinoma  
**Protocol Number:** WSU-C-2232, NCI-WSU-910  
**Participating Institution:** Barbara Ann Karmanos Cancer Institute, Wayne State University  
**Protocol Status:** Active  
**Contact:** Maha Hadi A. Hussain, MD, (313) 745-2357 or (313) 745-8296  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Title:** Phase II Study of Fenretinide in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck  
**Protocol Number:** MDA-ID-99334, NCI-610  
**Participating Institution:** M. D. Anderson Cancer Center  
**Protocol Status:** Active  
**Contact:** Fadlo R. Khuri, MD, (713) 792-6363  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Title:** Phase II Study of Fenretinide in Patients With Recurrent or Metastatic Ovarian Epithelial or Primary Peritoneal Cancer  
**Protocol Number:** CHNMC-PHII-25, LAC-USC-5GYN003  
**Participating Institutions:** Norris Comprehensive Cancer Center and Hospital, University of Southern California, Los Angeles; City of Hope Medical Center, Duarte, California; City of Hope Medical Group, Inc, Pasedena, California; University of California Davis Cancer Center, Sacramento  
**Protocol Status:** Approved  
**Contact:** Agustin A. Garcia, MD, (626) 359-8111 ext 3029 or (323) 865-0470  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)  

**Phase I**

**Title:** Phase I Study of Fenretinide, Paclitaxel, and Cisplatin in Patients With Refractory Solid Tumors  
**Protocol Number:** OSU-00H0186, NCI-2530  
**Participating Institutions:** Arthur G. James Cancer Hospital, Ohio State University Hospital; Wayne State University  
**Protocol Status:** Active  
**Contact:** Gregory Otterson, MD, (614) 293-6786  
**Latest Information:** [http://cancernet.nci.nih.gov/](http://cancernet.nci.nih.gov/)

**Title:** Phase I Study of Fenretinide, Paclitaxel, and Cisplatin in Patients With Advanced Solid Tumors  
**Protocol Number:** CWRU-3Y99, NCI-T99-0098  
**Participating Institutions:** Ireland Cancer Center, Cleveland, Ohio; University of Pittsburgh Cancer
Institute

Protocol Status: Active

Contact: Beth A. Overmoyer, (216) 844-8573 or (216) 844-5176

Latest Information: http://cancernet.nci.nih.gov/

References:


