

NANT 2004-04: Fenretinide (4-HPR, NSC 374551) Lym-X-Sorb™ (LXS) Oral Powder In Patients with Recurrent or Resistant Neuroblastoma

Basic Study Information

Type of Trial	Status of Trial	Age Range (yrs.)	Sponsor of Trial	Protocol ID
Treatment	Active	≤ 30	NANT	NANT 2004-04

Outline

Fenretinide (N-(4-hydroxyphenyl)retinamide, 4-HPR), is a cytotoxic retinoid that has activity against neuroblastoma cell lines in vitro in a dose-related manner. Fenretinide has proven clinical tolerability at plasma doses of 1 - 18 µM when given orally using a 100 mg capsule (NCI, IND#40294). However, the current 4-HPR oral capsule has low bioavailability, produces wide interpatient variability in peak and steady-state plasma levels, and is difficult to deliver in patients <4 years of age. Thus, 4-HPR pharmacokinetics and tumor response may benefit from an improved formulation of delivery. In an attempt to improve the antitumor activity of 4-HPR, a novel oral 4-HPR powder formulation (4-HPR / LXS oral powder, ~3% by weight 4-HPR) has been prepared based on a lipid matrix technology, called Lym-X-Sorb™ (LXS). 4-HPR/LXS oral powder is suitable for delivery in non-milk fat-containing foods, and especially as a slurry in non-milk fat-containing, or soy-based nutritional supplements, such as Slim-Fast Meal". We hypothesize that 4-HPR / LXS oral powder will: 1) allow drug administration to patients intolerant of the current NCI 4-HPR capsule, 2) produce more consistent, and possibly higher, 4-HPR plasma levels resulting in increased drug delivery to tumor cells, and 3) facilitate the testing of Fenretinide-based drug combinations. In the present study, modeled after the current COG Phase II oral 4-HPR capsule study in recurrent/resistant neuroblastoma (ANBL0321), patients will receive 4-HPR/LXS oral powder, BID x 7 days, every three weeks. PRIMARY STUDY AIMS are to define the maximally tolerated dose (MTD) and toxicity profile of 4-HPR/LXS oral powder, and the pharmacokinetics of 4-HPR when given in 4-HPR / LXS oral powder, in pediatric patients with relapsed / refractory neuroblastoma. SECONDARY STUDY AIMS are to assess the bioavailability of 4-HPR in 4-HPR/LXS oral powder in peripheral blood mononuclear cells. Levels of 4-HPR, and its metabolite, 4-MPR, will be determined in peripheral blood mononuclear cells (PBMC) six hours after the AM dose of 4-HPR/LXS oral powder on Day 6 of the Second Course.

Objectives

The **primary goals** of this research study are:

- To determine the maximum tolerated dose of Fenretinide (4-HPR, NSC 374551) Lym-X-Sorb™(LXS) Oral Powder (4-HPR/LXS oral powder) given orally, BID, for seven consecutive days every three weeks, in patients with recurrent and/or resistant neuroblastoma.
- To define the toxicities of 4-HPR/LXS oral powder given on this schedule.
- To determine the plasma pharmacokinetics of 4-HPR given on this schedule.

The **secondary goals** of this research study are:

- To determine the response rate to 4-HPR/LXS oral powder in patients with recurrent and/or resistant neuroblastoma within the confines of a Phase I study.
- To determine the level of 4-HPR delivered as 4-HPR/LXS oral powder in normal peripheral blood mononuclear cells (PBMC) as a tumor cell surrogate tissue.

Projected Accrual

NANT expects to accrue 12 patients per year, which will permit completion of the study within 2 ½ years.

Entry Criteria

Age

- Patients must be less than or equal to 30 years of age inclusive when registered on study.

Diagnosis

- Patients must have a diagnosis of neuroblastoma either by histologic verification of neuroblastoma and/or demonstration of tumor cells in the bone marrow with increased urinary catecholamines.

Disease Status

- Patients must have high-risk neuroblastoma with at least ONE of the following:
 - Recurrent/progressive disease at any time.
 - Refractory disease (i.e. less than a partial response to frontline therapy). No biopsy is required for eligibility for study.
 - Persistent disease after at least a partial response to frontline therapy (i.e. patient has had at least a partial response to frontline therapy but still has residual disease by MIBG, CT/MRI, or bone marrow). Patients in this category are REQUIRED to have a biopsy of at least one residual site demonstrating viable neuroblastoma.
 - Patients must have at least ONE of the following sites of disease:
 - Measurable tumor on MRI or CT scan or X-ray. Measurable is defined as minimum 20 mm in at least one dimension; for spiral CT defined as minimum of 10 mm in at least one dimension. For patients with persistent disease, a biopsy of bone and/or soft tissue site seen on CT/MRI must have been done to demonstrate viable neuroblastoma. If lesion was radiated, biopsy must be done at least 2 weeks after radiation completed.
 - MIBG scan with positive uptake at minimum of one site. For patients with persistent disease, a biopsy of an MIBG positive site must have been done to demonstrate viable neuroblastoma. If lesion was radiated, biopsy must be done at least 2 weeks after radiation completed
 - Bone marrow with tumor cells seen on routine morphology (not by NSE staining only) of bilateral aspirate and/or biopsy on one bone marrow sample.
 - CNS lesions: Patients with parenchymal or extradural CNS lesions that are present at study entry evaluation are NOT eligible. Skull lesions are eligible so long as there is no intracranial soft tissue extension. Patients with a history of complete surgical resection of CNS lesions are eligible if there is no evidence of CNS lesions at study entry evaluation and if other entry criteria are met. Patients with prior history of CNS irradiation are study eligible.
- Performance Level and Life Expectancy: Patients must have a performance status of 0, 1 or 2. Patients

who are unable to walk because of paralysis or tumor pain, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. Patients must have a life expectancy of ≥ 2 months.

Prior Therapy

- Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

Myelosuppressive chemotherapy and/or biologics:

- Must not have received within 3 weeks of entry onto this study (4 weeks if prior nitrosourea).
 - XRT: Patients must not have received radiation for a minimum of two weeks prior to study entry at the site of any lesion that was biopsied to document study eligibility or if radiation was given to only site of measurable disease. A minimum of six weeks is required following prior large field radiation therapy (i.e. TBI, craniospinal therapy, whole abdomen, total lung, >50% marrow space)
 - Stem Cell Transplant (SCT) or support: Patients are eligible three months after autologous stem cell transplant if hematological and all other criteria are met. Patients status post allogeneic stem cell transplant are NOT eligible.
 - Prior MIBG therapy: A minimum of six weeks is required following prior therapeutic doses of MIBG.
 - Study specific limitations on prior therapy: There is no limit on number of prior regimens.
 - Growth factor(s): Must not have received any hematopoietic growth factors within 7 days of study entry.
 - Organ Transplant: Patients may NOT be the recipient of an organ transplant.
 - Study specific limitations on prior therapy: NO prior Fenretinide therapy. Prior therapy with other retinoids is allowed.

Concomitant Therapy Restrictions

- Patients must NOT receive other anti-cancer agents while on study.
- Palliative radiation is allowed to sites that will not be used to measure response during this study.
- Patients should NOT receive supplemental Vitamin A, C, or E except as contained in routine total parenteral nutrition vitamin supplements, or in a single daily standard dose oral multivitamin supplement, because of possible interference with antitumor 4-HPR-induced, reactive oxygen species and/or ceramide, and due to the unknown effects of these drugs on retinol levels.
- Patients must NOT take any drugs suspected of causing pseudotumor cerebri, which include tetracycline, nalidixic acid, nitrofurantoin, phenytoin, sulfonamides, lithium, amiodarone, or vitamin A (except as part of routine TPN supplements or as part of a single daily standard dose oral multivitamin supplement).
- Concomitant use of herbal supplements or other alternative therapy medications IS CONTRAINDICATED due to potential adverse metabolic interactions of such supplements with Fenretinide.
- Patients should NOT concurrently take medications that may potentially act as modulators of intracellular ceramide levels or ceramide cytotoxicity, sphingolipid transport, or p-glycoprotein (MDR1) or MRP1 drug/lipid transporters, such as: cyclosporine A or analogue; verapamil; tamoxifen or analogue; ketoconazole, chlorpromazine; RU486; indomethacin; or sulfipyrazone. Contact Study Chair if there are questions regarding the suitability of any medication.

- As corticosteroids may impact sphingolipid metabolism, corticosteroids should NOT be used for emesis control during the course of the study. Systemic corticosteroids for asthma control should be minimized. Inhaled corticosteroids for asthma control are allowed. Steroids for routine metabolic deficiency states are allowed.

Organ Function Requirements: All patients must have adequate organ function defined as:

- Hematologic Function:** As it is not known if Fenretinide at doses potentially achievable by the present 4-HPR/LXS oral powder formulation causes hematopoietic toxicity, the following criteria must be met by all patient regardless of bone marrow involvement by tumor:
 - Hemoglobin \geq 8.0. Must be transfusion independent, defined as at least two weeks since last transfusion
 - ANC: \geq 750. Must be at least 7 days after last dose of growth factor
 - Platelet count: \geq 75,000. Must be transfusion independent, defined as at least two weeks since last platelet transfusion
- Renal function:** Age-adjusted serum creatine \leq 1.5x normal for age (see below)

Age	Maximum Serum Creatinine (mg/dL)
\leq 5 years	0.8
$>$ 5 years and \leq 10 years	1.0
$>$ 10 and \leq 15 years	1.2
$>$ 15 years	1.5

- Cardiac Function:** Patient must have normal cardiac function documented by:
 - ejection fraction ($>$ 55%) documented by echocardiogram or radionuclide MUGA evaluation OR
 - fractional shortening ($>$ 27%) documented by echocardiogram AND
 - EKG must demonstrate no abnormality severe enough to justify cardiac medications
- Liver Function:**
 - Total bilirubin \leq 1.5 x normal for age, AND
 - SGPT (ALT) and SGOT (AST) \leq 3 x normal for age
- Central Nervous System Function:** Patients with a seizure disorder are study eligible if seizures are controlled on anticonvulsants and if the specific anticonvulsant(s) is not contraindicated.
- Pulmonary Function:** Normal lung function as manifested by no dyspnea at rest or exercise intolerance and no oxygen requirement.
- Reproductive Function:** Due to the potential teratogenic effects of retinoids, negative serum beta-HCG in females, and use of effective contraception in males and females of child-bearing potential, is required.
- Skin toxicity no greater than grade 1 per CTCAE v3.
- Serum triglycerides $<$ 300mg/dL.
- Serum calcium $<$ 11.6mg/dL.

- No hematuria and/or proteinuria greater than 1+ on urinalysis.
- Patients with known genetic metabolic conditions, or other ongoing serious medical issues.

Exclusion Criteria

- Pregnancy or breast feeding. Due to the potential teratogenic effects of retinoids, pregnant women are NOT eligible. Breast milk feeding by study patient is NOT allowed.
- Patients with history of organ and allogeneic stem cell transplants.
- Patients with a known history of allergy to soy products.
- Patients with a known history of a severe allergy or sensitivity to wheat gluten.
- Patients requiring anti-arrhythmia cardiac medications are NOT eligible.
- Patients with specific CNS lesions.
- Patients with prior therapy with Fenretinide. Other retinoids are allowed.
- Patients who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.

Who should I contact for more information?

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