Study: NANT 2012-01

DFMO, Celecoxib with Cyclophosphamide and Topotecan for patients with Relapsed or Refractory Neuroblastoma

Protocol Title:
Phase I Study of difluoromethylornithine (DFMO) and celecoxib with cyclophosphamide/topotecan for patients with relapsed or refractory neuroblastoma

Study Chair: Michael Hogarty, MD Children's Hospital of Philadelphia

What is this study about:

This study will combine an oral drug called DFMO with celecoxib (also oral) and two IV chemotherapy medicines called cyclophosphamide and topotecan.

DFMO is an investigational drug that is not approved by the FDA for use in cancer patients, although it has been approved by the FDA for use against an infection called trypanosomiasis that can affect the brain. DFMO blocks the production of chemicals called polyamines that are important in the growth of cancer cells. This drug has been tested by itself, and combined with chemotherapy, in adults with cancer and has had limited activity. It has not been tested in combination with celecoxib and chemotherapy in patients with childhood tumors. It is believed that polyamines may play a more important role in childhood tumors, particularly those that depend on the abnormal activity of MYC genes. In the laboratory, DFMO and celecoxib are able to reduce the growth of neuroblastoma tumors using models of this cancer in mice. This effect is even greater when DFMO and celecoxib are combined with chemotherapy drugs, including cyclophosphamide and topotecan.

Celecoxib is a non-steroidal anti-inflammatory medication that is FDA approved for inflammation associated conditions but not for cancer. It is given at the same dose and schedule as it would be used for inflammation. It has been shown to cooperate with DFMO to affect polyamine levels in cells.

Cyclophosphamide and topotecan are both FDA-approved chemotherapy drugs. These drugs are approved for the treatment of certain adult cancers, but have also been used to treat children with cancer, including many children with neuroblastoma. In some patients with neuroblastoma, even some that have relapsed after prior chemotherapy, this combination reduces the amount of neuroblastoma.

Giving DFMO and celecoxib together with cyclophosphamide and topotecan may increase the effectiveness of this combination. We first need to find out the highest dose of DFMO that can be given safely together with celecoxib, cyclophosphamide and topotecan. This study will be the first study to test giving DFMO together with these drugs. Once we have found out the highest dose of DFMO that can be given with celecoxib, cyclophosphamide and topotecan, we will treat more patients with this combination to determine how safe and effective it is.

Why is this study being done:

- To find the highest dose of DFMO that can be given with celecoxib, cyclophosphamide and topotecan without causing severe side effects.
- To find out the side effects seen by giving DFMO at different dose levels with celecoxib, cyclophosphamide and topotecan.
- To measure the levels of DFMO in the blood at different dose levels.
- To determine if your tumor gets smaller after treatment with DFMO, celecoxib, cyclophosphamide and topotecan.
- To determine if specific gene changes in you or your tumor makes you more prone to side effects or affects your tumor's response to the combination of DFMO, celecoxib, cyclophosphamide and topotecan.

- To determine if the amount of normal chemicals in your body called polyamines go down in response to DFMO, celecoxib, cyclophosphamide and topotecan, and whether you are more likely to have a good response to the treatment if they do.

Criteria that need to be met to participate in this study:

- Patients must be ≥ 2 years and ≤ 30 years of age when registered on study.

- Patients must have recurrent/progressive high-risk neuroblastoma, refractory high-risk neuroblastoma that had less than a partial response to standard treatment or persistent high-risk neuroblastoma that had at least a partial response to standard treatment. All patients must have at least ONE site of evaluable disease.

- Patients must have adequate heart, kidney, liver and bone marrow function. Patients who have bone marrow disease must still have adequate bone marrow function to enter the study.

- Patients with other ongoing serious medical issues must be approved by the study chair prior to registration.

The following patients cannot participate in the study :

Females of childbearing potential that do not have a negative pregnancy test.

Patients that are pregnant, breast feeding, or unwilling to use effective contraception during the study

Patients status post allogeneic stem cell transplant.

Patients who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.

Patients with disease of any major organ system that would compromise their ability to withstand therapy.

Patients who are on hemodialysis.

Patients with an active or uncontrolled infection. Patients on prolonged antifungal therapy are still eligible if they are culture and biopsy negative in suspected radiographic lesions and meet other organ function criteria.

Patients who have had a seizure within 12 months prior to enrollment and patients receiving anti-convulsant therapy for a seizure disorder.

Patients with known Aspirin-Hypersensitivity triad (asthma, allergic rhinitis, ASA hypersensitivity).

Study procedures:

This study will test up to 4 DFMO doses with fixed doses of celecoxib, cyclophosphamide and topotecan in groups of 3-6 patients, which will be assigned upon enrollment. The starting DFMO dose for the first group of patients is approximately 33% of the dose recommended for use adults.

Each treatment course is 28 days with the exception of the first cycle which will have a lead in of 7 days when patients will only receive DFMO and celecoxib.
This diagram outlines one course of therapy on this study:

Drug Administration

7 day lead-in Cycle 1 and before any later cycle if therapy has been interrupted >14 days

Cycle 1 *

Day	1-7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22-28
Cyclophosphamide		X	X	X	X	X										
Topotecan		X	X	X	X	X										
DFMO	X	X	X	X	X	X	X	X								X
Celecoxib	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Growth factor support using G-CSF or pegylated-G-CSF is required.

Cycles 2 through 17*

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Cyclophosphamide	X	X	X	X	X																
Topotecan	X	X	X	X	X																
DFMO	X	X	X	X	X	X	X								X	X	X	X	X	X	X
Celecoxib	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Patients will have their neuroblastoma evaluated by bone marrow tests and scans after finishing two cycles of this treatment and then again after the 4th cycle, and then every fourth cycle. Each cycle is 21 days, with the exception of cycle 1 which is 28 days.

Patients may receive up to 17 cycles of therapy (~1 year) on study in the absence of progressive disease. Decisions regarding additional therapy on this study will be made by the study chair and treating physician in collaboration with the NANT Medical Director.

If you are interested in getting more information about this clinical trial, please email us at nantops@chla.usc.edu.