Study: NANT 2011-04

Lenalidomide, Anti-GD2 Mab Ch14.18 and 13-Cis-Retinoic Acid in Recurrent or Resistant Neuroblastoma Patients

Protocol Title: A Phase I Study Of Lenalidomide And Anti-GD2 Mab Ch14.18 +/- 13-Cis-Retinoic Acid in Patients With Refractory/Recurrent Neuroblastoma.

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What is this study about:

This study will combine three drugs; lenalidomide, Ch14.18 and 13-cis-retinoic acid. Patients may have taken 1 or all of these medicines before (but not together) for treatment of their neuroblastoma. Patients may be able to receive this therapy if they have taken these medicines before.

Ch14.18 is a monoclonal antibody. Monoclonal antibodies are proteins made in the lab, designed to attach to specific targets on cancer cells. Ch14.18 was designed to attach to neuroblastoma cells and other cancer cells that have GD-2 on their cells. When ch14.18 attaches to the neuroblastoma cells, the body's immune system is stimulated to attack and kill the neuroblastoma cells. Ch14.18 represents a new kind of cancer therapy that, unlike chemotherapy and radiation, targets the killing of cancer cells without destroying nearby healthy cells.

13-cis-retinoic acid (Accutane®, cisRA or Isotretinoin) works as a continuing treatment to maintain the response to previous treatments. 13-cis-retinoic acid is a drug closely related to vitamin A and has been shown to help change the remaining neuroblastoma (cancer) cells into normal nerve cells. It is commercially available for use in neuroblastoma.

A recently completed study that compared the experimental immunotherapy regimen ch14.18 with 13-cis-retinoic acid and 2 other medications called cytokines to 13-cis-retinoic acid alone showed that the experimental treatment worked better than standard treatment to help get rid of any remaining neuroblastoma cells.

In this study, lenalidomide is being given instead of the other two cytokines to see if the side effects will be less than on the prior studies. We are also trying to see if this combination will work on the immune system in the same or better way than the other combinations that have been used.

Lenalidomide is an oral medication that has been approved by the Food and Drug Administration (FDA) for the treatment of other cancers, including multiple myeloma. We are using lenalidomide because it seems to work against cancer in test tubes and animals and has been used and safely given to children with solid tumors. It affects some of the ways the immune system functions and recognizes tumor, and appears to work by slowing or stopping the growth of new cancer cells. For the purposes of this study, Lenalidomide is considered experimental.

This is the first study to test giving these three drugs together and will help determine the highest doses of lenalidomide that can safely be given together with Ch14.18 and 13-cis-retinoic acid to patients with resistant/relapsed neuroblastoma.

Why is this study being done:

- To find the highest doses of lenalidomide in combination with fixed doses of ch14.18 and 13-cis-retinoic acid that can be given to children with refractory or recurrent neuroblastoma without causing severe side effects

- To learn about the side effects of giving of lenalidomide together with ch14.18 and 13-cis-retinoic acid.
- To learn about the differences in immune function when giving different doses of lenalidomide given with ch14.18 and 13-cis-retinoic acid.

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

- Patients must be ≤ 21 years of age when registered on study.

- Patients must have relapsed neuroblastoma, refractory neuroblastoma that had less than a partial response to standard treatment or persistent neuroblastoma that had at least a partial response to standard treatment.

    - Patients with a history of relapse with no evaluable disease may enroll as long as they have not been off therapy for greater than 3 months.

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

- Lenalidomide must be swallowed as whole capsules. Therefore, patients must be able to swallow pills to be eligible for study. The smallest capsule is the size of half an M&M and the largest about the size of a whole peanut.

Patients cannot participate in the study if:

- They were previously treated with anti-GD2 antibody therapy and had tumor relapse/progression while receiving this therapy.

- They have received 13-cis-retinoic acid and lenalidomide together.

- They have other medical problems that could get much worse if they had this treatment.

- They are pregnant or breast feeding.

- They have a history of a venous or arterial thrombosis that was not associated to a central line.

- They have active infections such as hepatitis or fungal infections.

- They have brain metastasis at study entry.

- They have had an allogeneic stem cell transplant (received stem cell from someone else)

- They can't cooperate with the special precautions that are needed for this trial.

Study procedures:

This study will test up to 4 Lenalidomide doses with fixed doses of ch14.18 and 13-cis-Retinoic in groups of 3-6 patients, which will be assigned upon enrollment. The starting Lenalidomide dose for the first group of patients is approximately 80% of the highest dose previously tested in children when given without other drugs.

At the beginning of the study, a few patients will be treated with a lower dose of lenalidomide and standard dose ch14.18. The first patients on this study will not receive 13-cis-retinoic acid. If these doses do not cause bad side effects, the lenalidomide doses will slowly be made higher, and 13-cis-retinoic acid will be added. Once 13-cis-retinoic acid is added, all patients will receive the same dose of that drug.

Each treatment course is 28 days. You may receive up to 12 courses of therapy as long you are benefiting from treatment and continue to meet the criteria to continue safely on this study.

This diagram outlines one course of therapy on this study:

DAY OF COURSE:				
Days 1-7	8-11	12-14	15-21	22-28
Lenalidomide	Lenalidomide	Lenalidomide	Lenalidomide (Levels 1-6 only)**	Rest
	Ch14.18			
			13-cis-retinoic acid* (Levels 2-6 only)	13-cis-retinoic acid* (Levels 2-6 only)

The study consent form includes a comprehensive list of potential side effects of these drugs. Some of the most common potential side effects are pain from the infusion, allergic reactions to the infusion including hives and blood pressure changes, fewer red blood cells in the blood, diarrhea, inflammation or sores in the mouth or make swallowing difficult, nausea, vomiting, extreme tiredness, joint pains, sun sensitivity, low numbers of white blood cells (that make it easier to get infections which may be life threatening), fewer platelets in the blood (the type of cells that help your blood clot), increased in fats and calcium in your blood.

After the highest dose of lenalidomide that can be given safely with ch14.18 and 13-cis-retinoic acid has been determined, 20 additional patients may be treated to obtain further information on the side effects of these drugs given together and their effects on neuroblastoma tumors. This part of the study is called the Expansion Cohort part of the study, which will allow patients with no evaluable or measurable tumor to enter.

This regimen will require in-patient hospitalization during the time Days 8-12.

Patients will have their neuroblastoma evaluated by bone marrow tests and scans after finishing two courses of this treatment (around 8 weeks after starting) and then again after the 4^{th}, 6^{th} , and 9^{th} courses. Patients will also be evaluated at the completion of therapy.

Patients may receive up to 12 cycles of therapy (~12 months) on study in the absence of progressive disease or bad side effects.