NANT 2011-04: A Phase I Study of Lenalidomide and Anti-GD2 Mab Ch14.18 +/- Isotretinoin in Patients With Refractory/Recurrent Neuroblastoma

PURPOSE: This phase I trial studies the side effects and best dose of lenalidomide when given together with monoclonal antibody with or without isotretinoin in treating younger patients with refractory or recurrent neuroblastoma. Drugs used in chemotherapy, such as lenalidomide and isotretinoin, work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing. Monoclonal antibodies, such as monoclonal antibody Ch14.18, can block tumor growth in different ways. Some block the ability of tumor cells to grow and spread. Others find tumor cells and help kill them or carry tumor-killing substances to them. Giving more than one drug (combination chemotherapy) together with monoclonal antibody therapy may kill more tumor cells.

Study Type: Interventional
Masking: Open Label
Primary Purpose: Treatment

OBJECTIVES:

PRIMARY OBJECTIVES:

I. To determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) of lenalidomide in combination with fixed doses of ch14.18 (monoclonal antibody Ch14.18) given intravenously (IV) for four days (days 8-11) and isotretinoin given twice each day orally for 14 days (days 15-28) and repeated every 28 days to children with refractory or recurrent neuroblastoma.

II. To define the toxicities of lenalidomide administered in combination with ch14.18 and isotretinoin.

III. To describe the differences in immune function modulation between "low" versus "high" dose lenalidomide given with ch14.18 and isotretinoin.

SECONDARY OBJECTIVES:

I. To determine the pharmacokinetics of lenalidomide given in this combination regimen.

II. To determine the steady state pharmacokinetics of isotretinoin (day 28, course one) given in combination with lenalidomide.

III. To measure peak and trough levels of ch14.18 in patients receiving lenalidomide and to compare to historical controls of patients receiving ch14.18 in combination with interleukin 2 (IL-2) and sargramostim (GM-CSF).

IV. To describe the immunological effects of lenalidomide (T cells, natural killer (NK) cells, monocytes, cytokines, chemokines) within this three drug regimen.

V. To define the incidence and titers of human anti-chimeric antibody (HACA) on this regimen.

VI. To describe, within the context of a phase I study, the response rate to lenalidomide combined with ch14.18 and isotretinoin in patients with recurrent/refractory neuroblastoma.

VII. To quantify neuroblastoma tumor cell "load" using a 5-gene TaqMan Low Density Array (TLDA) assay in peripheral blood at study entry, following, with each disease evaluation and at end of therapy.
and bone marrow at study entry, with each response evaluation when bone marrow is sampled, and at end of therapy.

IX. To compare the toxicities of this regimen with the historical toxicity data from the Children's Oncology Group (COG) ANBL0032 and ANBL0931 studies of ch14.18 with IL-2, GM-CSF and isotretinoin.

OUTLINE: This is a dose-escalation study of lenalidomide.

Patients receive lenalidomide orally (PO) once daily (QD) on days 1-21, monoclonal antibody Ch14.18 IV over 10 hours on days 8-11, and isotretinoin PO twice daily (BID) on days 15-28 of dose levels 2-5. Treatment repeats every 28 days for up to 6 courses in the absence of disease progression or unacceptable toxicity.

After completion of study treatment, patients are followed up periodically.

AGES ELIGIBLE FOR STUDY: up to 21 Years

CRITERIA

Inclusion Criteria:

- 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

- Patients must have high-risk neuroblastoma

- Disease Status:
  - Recurrent/progressive disease at any time - regardless of response to frontline therapy
  - Refractory disease (i.e. less than a partial response to frontline therapy, including a minimum of 4 cycles of chemotherapy)
  - Persistent disease after at least a partial response to frontline therapy: i.e. patient has had a partial response to frontline therapy but still has residual disease AND has never had a relapse/disease progression
  - Patients must have at least ONE of the following (excluding those patients entered in the expansion cohort who may be entered on study with no measurable or evaluable tumor if they have had a prior progression):
    - At least one metaiodobenzylguanidine (MIBG) avid bone site or diffuse MIBG uptake
    - Any amount of neuroblastoma tumor cells in the bone marrow based on routine morphology (with or without immunocytochemistry) in at least one sample from bilateral aspirates and biopsies; note: patients with < 10% tumor on all samples from bilateral bone marrow aspirates/biopsies are eligible, but will be considered separately in definitions of bone marrow response
At least one measurable soft tissue site on magnetic resonance imaging (MRI)/computed tomography (CT) scan that is MIBG or positron emission tomography (PET) avid (if patient known to be MIBG non-avid); measurable is defined as >= 10 mm in at least one dimension

At least one measurable soft tissue site on MRI/CT scan that is non-avid by MIBG and PET but that meets either one of the following criteria:

- The lesion has been biopsied at any time point in the past and was documented to be neuroblastoma AND the lesion has enlarged since the immediate prior therapy by a minimum of 20% in at least one dimension
- If the lesion is stable or smaller since the last prior therapy then a biopsy must be performed at least three weeks after the last day of the last prior therapy that shows neuroblastoma or ganglioneuroblastoma

Patients must have a life expectancy of at least 6 weeks and a Lansky (<= 16 years) or Karnofsky (> 16 years) score of at least 50

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

Patients must not have received the therapies indicated below for the specified time period prior to the first day of administration of protocol therapy on this study

- Myelosuppressive chemotherapy: must have received last dose at least 2 weeks prior to protocol therapy; this includes cytotoxic agents given on a low dose metronomic regimen
- Biologic (anti-neoplastic agent) (includes retinoids): must have received last dose at least 7 days prior to protocol therapy
- Monoclonal antibodies: must have received last dose at least 7 days or 3 half-lives, whichever is longer, prior to protocol therapy

Radiation:

- Patients must not have received radiation (small port) for a minimum of two weeks prior to protocol therapy; for patients with only one site of measurable or evaluable disease, radiation must not have been given to that site unless that site has demonstrated clear progression after radiation, or a biopsy of the site demonstrated neuroblastoma at least 3 weeks after the last day of radiation
- A minimum of 12 weeks prior to start of protocol therapy is required following large field radiation therapy (i.e. total body irradiation, craniospinal, whole abdominal, total lung, > 50% marrow space)
- A minimum of 6 weeks must have elapsed prior to start of protocol therapy for other substantial bone marrow radiation

Stem Cell Transplant (SCT):

- Patients are eligible 6 weeks after date of autologous stem cell infusion following myeloablative therapy (timed from first day of protocol therapy)
Patients are not eligible post allogeneic stem cell transplant

- Patients who have received an autologous stem cell infusion to support non-myeloablative therapy (such as 131 iodine [I]-MIBG) are eligible at any time as long as they meet the other criteria for eligibility

- A minimum of 6 weeks must have elapsed after 131I-MIBG therapy prior to start of protocol therapy

- Prior anti-GD2 antibody, isotretinoin, or lenalidomide therapy:
  - Patients who have received prior anti-GD2 antibody therapy are eligible if they did not have tumor relapse/progression while receiving this therapy
  - Patients who have received either isotretinoin or lenalidomide are eligible, but not if they have received the two agents concomitantly

- All cytokines or hematopoietic growth factors must be discontinued a minimum of 7 days prior to protocol therapy

- Patients must not be receiving any other anti-cancer agents or radiotherapy at the time of study entry or while on study

- Absolute phagocyte count (APC = neutrophils and monocytes): >= 1000/mm3

- Absolute neutrophil count: >= 750/mm3

- Platelet count: >= 50,000/mm3, transfusion independent (no platelet transfusions within 1 week)

- Hemoglobin >= 8.0 (may transfuse)

- Patients with known bone marrow metastatic disease will be eligible for study as long as they meet hematologic function criteria; patients with marrow disease are not evaluable for hematologic toxicity

- Age-adjusted serum creatinine <= 1.5 x normal for age AND creatinine clearance or glomerular filtration rate (GFR) >= 60cc/min/1.73m2

- <= grade 2 hematuria (criteria applicable only for dose levels that include isotretinoin) and <= grade 2 proteinuria

- Total bilirubin <= 1.5 x upper limit of normal for age

- Serum glutamic pyruvate transaminase (SGPT) (alanine aminotransferase [ALT]) <= 135 and serum glutamic oxaloacetic transaminase (SGOT) (aspartate aminotransferase [AST]) < 3 x upper limit of normal (note that for ALT, the upper limit of normal is defined as 45 U/L)

- Sinusoidal obstruction syndrome (SOS) if present, must be stable or improving clinically

- Cardiac function:
  - Normal ejection fraction (>= 55%) documented by either echocardiogram or radionuclide multi gated acquisition scan (MUGA) evaluation;
  - OR
Normal fractional shortening (>= 27%) documented by echocardiogram

- No dyspnea at rest
- Serum triglyceride =< 300mg/dL (applicable only for dose levels that include isotretinoin) (note that a non-fasting triglyceride value could be obtained, if this is > 300 mg/dL then a fasting triglyceride should be obtained and patient will be eligible if the fasting level is < 300 mg/dL)
- =< grade 2 hypercalcemia (applicable only for dose levels that include cis retinoic acid [RA])
- All post-menarchal females must have a negative beta-human chorionic gonadotropin (HCG); males and females of reproductive age and childbearing potential must use effective contraception for the duration of their participation
- Patients with other ongoing serious medical issues must be approved by the study chair prior to registration

Exclusion Criteria:

- Serum b-HCG must be negative in girls who are post-menarchal; males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method; pregnant or breast-feeding women will not be entered on this study
- Breast feeding women are not eligible
- Patients who have an active or uncontrolled infection are excluded
- Patients with a paraben allergy cannot take isotretinoin preparations containing this compound (ie Accutane, Sotret) but are eligible if they can take an alternate preparation without paraben; (applicable only for entry onto dose levels receiving isotretinoin)
- Patients with a history of venous or arterial thrombosis personally or in a first degree relative before the age of 40 years unless associated with a central line
- Prior allogeneic transplant
- Patients with a history of prior central nervous system (CNS) metastases or skull lesions with intracranial extension will be required to have a head CT or MRI at study entry demonstrating no active CNS metastases; patients with skull metastases with associated intracranial soft tissue masses will remain eligible
- Inability to swallow lenalidomide capsules whole; capsules of 13-isotretinoin may be opened

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