

NANT 2008-02: Phase I Study of Vorinostat in Combination With 13-Cis-Retinoic Acid in Patients With Refractory/Recurrent Neuroblastoma

Rationale

Vorinostat may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. Isotretinoin may help vorinostat work better by making tumor cells more sensitive to the drug. Giving vorinostat together with isotretinoin may be an effective treatment for neuroblastoma.

Purpose

This phase I trial is studying the side effects and the best dose of vorinostat when given together with isotretinoin to see how well it works in treating patients with high-risk refractory or recurrent neuroblastoma.

Objectives

Primary

- To determine the maximum-tolerated dose of vorinostat in combination with isotretinoin in patients with high-risk refractory or recurrent neuroblastoma.
- To define the toxicity of this regimen in these patients.

Secondary

- To determine the pharmacokinetics of vorinostat suspension in these patients.
- To describe the relationship of vorinostat pharmacokinetics with the occurrence of systemic toxicity.
- To describe histone acetylation levels in peripheral blood mononuclear cells after different doses of vorinostat.
- To describe the response to this regimen in these patients.
- To describe the toxicity of this regimen in patients who are 22-30 years of age.
- To describe the response rate in patients 22-30 years of age treated with this regimen.

Outline

This is a multicenter, dose-escalation study of vorinostat.

Patients receive oral isotretinoin twice daily on days 1-14, oral suspension* of vorinostat once daily on days 1-4 of course 1, and oral capsules of vorinostat once daily on days 1-4 and 8-11 of course 2 and subsequent courses. Treatment repeats every 28 days for up to 12 courses in the absence of disease progression or unacceptable toxicity.

Expansion cohort 1 (≤ 21 years of age): Once the maximum-tolerated dose (MTD) has been determined, patients are treated at that dose level as above.

Expansion cohort 2 (22-30 years of age): Patients receive isotretinoin as above and vorinostat at the MTD on days 1-3 and 8-10. Treatment repeats every 28 days for up to 12 courses in the absence of disease progression or unacceptable toxicity.

Patients may undergo peripheral blood mononuclear cells collection for pharmacokinetics and histone acetylation studies.

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

NOTE: Patients less than 10 years of age are encouraged to continue to use oral suspension beyond course 1.

Eligibility

Ages Eligible for Study: up to 30 Years

Disease Characteristics

- Histologically confirmed high-risk neuroblastoma and/or demonstration of tumor cells in the bone marrow with increased urinary catecholamines meeting 1 of the following criteria:
 - Recurrent and/or progressive disease at any time
 - Biopsy not required
 - Refractory disease (i.e., less than a partial response to frontline therapy, including a minimum of 4 courses of chemotherapy)
 - Biopsy not required
 - Persistent disease by MIBG scan, CT and MRI scan, or bone marrow aspirates/biopsies after \geq partial response to frontline therapy
 - Histologic confirmation of viable neuroblastoma from at \geq 1 residual site required
 - Tumor seen on routine bone marrow morphology allowed
 - Bone marrow immunocytology alone not allowed
- Patients in expansion cohorts 1 and 2 who have had a prior relapse are eligible with no measurable or evaluable sites of tumor (i.e., in second complete response)
- Patient must have \geq 1 of the following disease sites (excluding patients on the expansion cohort):
 - Measurable tumor by MRI, CT scan, or X-ray
 - MIBG scan with positive uptake at a minimum of 1 site
 - Bone marrow with tumor cells seen on routine morphology of 1 bone marrow sample of a bilateral aspirate and/or biopsy

Patient Characteristics

- Life expectancy \geq 6 weeks
- Lansky performance status (PS) 50-100% (patients \leq 16 years of age) OR Karnofsky PS 50-100% (patients $>$ 16 years of age)
- Hemoglobin \geq 8 g/dL (transfusion allowed)
- ANC \geq 750/ μ L
 - ANC \geq 500/ μ L for patients with marrow metastases
- Platelet count \geq 50,000/ μ L (transfusion independent)
 - No platelet transfusions within 1 week
- Serum creatinine based on age as follows:
 - 0.8 mg/dL (\leq 5 years of age)

- 1.0 mg/dL (> 5 and ≤ 10 years of age)
- 1.2 mg/dL (> 10 and ≤ 15 years of age)
- 1.5 mg/dL (> 15 years of age)
- Hematuria ≤ 1+ and/or proteinuria ≤ 1+
- Total bilirubin ≤ 1.5 times upper limit of normal (ULN)
- ALT and AST < 3 times ULN
- Alkaline phosphatase ≤ 2.5 times ULN
- Serum triglycerides ≤ 300 mg/dL
- Serum calcium < grade 2
- Negative pregnancy test
- Not pregnant or nursing
- Fertile patients must use effective contraception
- Normal ejection fraction (≥ 55%) by echocardiogram or radionuclide MUGA OR normal fraction shortening (≥ 27%) by echocardiogram
- QTc interval ≤ 450 msec
- No patients who, in the opinion of the investigator, may not be able to comply with the safety of study requirements
- No disease of any major organ system that would compromise the patient's ability to withstand therapy
- No active or uncontrolled infection
 - Patients on prolonged antifungal therapy allowed provided culture and biopsy are negative in suspected radiographic lesions
- No allergic reactions to paraben preparations (i.e., Accutane, Sotret)
 - Alternate preparations to paraben allowed

Prior Concurrent Therapy

- Fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy
- At least 3 weeks since prior myelosuppressive chemotherapy, including cytotoxic agents given on a low-dose metronomic regimen
- At least 7 days since prior biologic anti-neoplastic agent (including retinoids) therapy
- At least 7 days or 3 half-lives, whichever is longer, since prior monoclonal antibodies
- More than 2 weeks since prior radiotherapy (small-port)
 - No prior radiotherapy in patients with 1 site of measurable or evaluable disease unless that site has demonstrated clear progression after completion of radiotherapy
 - At least 12 weeks since prior large-field radiotherapy (i.e., total-body, craniospinal, whole abdominal, total lung, or > 50% of marrow space irradiation)
 - At least 6 weeks since prior substantial bone marrow radiotherapy
- At least 6 weeks since prior:
 - Autologous stem cell infusion following myeloablative therapy
 - Allogeneic stem cell transplantation without evidence of active graft-versus-host disease
- At least 6 weeks since prior ¹³¹I-MIBG therapy
- At least 7 days since prior cytokines or hematopoietic growth factors
- More than 30 days since prior and no concurrent valproic acid
- More than 30 days since prior and no other concurrent investigational medications
- No prior vorinostat combined with isotretinoin
 - Prior vorinostat or isotretinoin single-agent or combined with alternative agents allowed

- No other concurrent anti-cancer agents including chemotherapy, radiotherapy, biologics, or immunomodulating agents
- No concurrent azole anti-fungal therapy
- No concurrent pentamidine therapy for PCP prophylaxis
- No concurrent enzyme-inducing anti-convulsant therapy

For more information contact:

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