

NANT 2007-03: Vorinostat With 131I-MIBG Therapy for Resistant/Relapsed Neuroblastoma: A Phase I Study

Type	Status	Age Range (yrs.)	Sponsor
Interventional	Active	2 to 30 years	CCHMC

Rationale

Vorinostat may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. Radioactive drugs, such as iobenguane I 131, may carry radiation directly to tumor cells and not harm normal cells. Giving vorinostat together with iobenguane I 131 may kill more tumor cells.

Purpose

This phase I trial is studying the side effects and best dose of giving vorinostat together with iobenguane I 131 in treating patients with resistant or relapsed neuroblastoma.

Objectives**Primary**

- To determine the maximum tolerated dose of vorinostat in combination with iobenguane I 131 in patients with resistant or relapsed neuroblastoma.
- To define the toxicities of vorinostat in combination with therapeutic doses of iobenguane I 131 in these patients.

Secondary

- To describe, within the context of a phase I study, the response rate in patients treated with vorinostat and iobenguane I 131.
- To describe histone acetylation levels and norepinephrine transporter mRNA levels in peripheral blood mononuclear cells after treatment with different doses of vorinostat.

Outline

This is a multicenter study.

Patients receive oral vorinostat once daily on days 1-14 and iobenguane I 131 IV over 1½-2 hours on day 3. Patients undergo autologous peripheral blood stem cell transplantation on day 17.

Blood samples may be collected periodically for correlative biological studies.

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

Eligibility

Ages Eligible for Study: 2 years-30 years

Disease Characteristics

- Diagnosis of neuroblastoma
- Histological confirmation and/or demonstration of tumor cells in the bone marrow with increased urinary catecholamines
- High-risk stage 3 OR metastatic disease
 - No stage 4S disease
- Meets ≥ 1 of the following criteria:
 - Recurrent or progressive disease at any time
 - Biopsy not required, even if partial response to intervening therapy
 - Refractory disease (i.e., less than a partial response to front-line therapy, including ≥ 4 courses of chemotherapy)
 - Biopsy not required
 - Persistent disease after at least a partial response to front-line therapy (i.e., patient has had at least a partial response to front-line therapy but still has residual disease by MIBG scan, CT scan/MRI, or bone marrow)
 - Biopsy (including bone marrow biopsy) of ≥ 1 residual site demonstrating viable neuroblastoma required
- Evidence of MIBG uptake into tumor site within the past 4 weeks and subsequent to any intervening therapy
- Adequate peripheral blood stem cells (PBSCs) available for autologous hematopoietic stem cell transplantation
 - At least 2×10^6 viable CD34+ cells/kg must be available (purged and unpurged)
 - Immunomagnetically purged PBSCs allowed
 - No CD34+ selected cells
 - No autologous stored umbilical cord blood stem cells
 - No allogeneic stem cells (other than PBSCs from an identical twin)

Patient Characteristics

- Lansky performance status (PS) 50-100% (for patients ≤ 10 years of age) OR Karnofsky PS 50-100% (for patients > 10 years of age)
- Life expectancy ≥ 6 weeks
- ANC $\geq 750/\mu\text{L}^*$
- Platelet count $\geq 50,000/\mu\text{L}^*$ (transfusion independent [i.e., no platelet transfusions within the past week])
- Serum creatinine ≤ 1.5 times normal for age as follows:
 - ≤ 0.8 mg/dL (for patients ≤ 5 years of age)
 - ≤ 1.0 mg/dL (for patients 6 to 10 years of age)
 - ≤ 1.2 mg/dL (for patients 11 to 15 years of age)
 - ≤ 1.5 mg/dL (for patients > 15 years of age)
- Total bilirubin ≤ 1.5 times normal for age
- ALT and AST < 3 times upper limit of normal (ULN) (for ALT, the ULN is defined as 45 U/L)
- Ejection fraction $\geq 55\%$ by ECHO or radionuclide MUGA OR fractional shortening $\geq 27\%$ by ECHO
- Corrected QT (QT_c) interval ≤ 450 msec

- Lung function normal (i.e., no dyspnea at rest, pleural effusion, or oxygen requirement)
- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use effective contraception
- Able to comply with the safety monitoring requirements of the study, in the opinion of the investigator
- Patient and family must be physically and psychologically able to cooperate with the radiation safety isolation guidelines
- Patient must not have a weight that would require exceeding a maximum total allowable dose of iobenguane I 131 at the assigned dose level (per institutional guidelines)
 - The study committee may discuss treating such patients at a lower dose level
- Other ongoing serious medical issues are allowed provided they have been approved by the study chair before registration
- No disease of any major organ system that would compromise the patient's ability to withstand study therapy
- No history of idiopathic deep venous thrombosis, pulmonary embolus, thrombotic stroke, or arterial thrombosis
- Patients with a history of central venous catheter-associated thrombosis that has completely resolved are eligible
- No active or uncontrolled infection
 - Patients on prolonged antifungal therapy are eligible provided they are culture and biopsy negative in suspected radiographic lesions and meet other organ function criteria
- No known HIV infection (testing not required before study entry)
- No active hepatitis B or C infection NOTE: *Regardless of bone marrow involvement with tumor

Prior Concurrent Therapy

- See Disease Characteristics
- Fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy
- No prior iobenguane I 131 therapy
- No prior vorinostat or other histone deacetylase inhibitors
- No prior allogeneic stem cell transplantation
- No prior total-body irradiation
- No prior radiotherapy to the sole site of measurable or evaluable disease unless that site has demonstrated clear progression after radiotherapy
- More than 12 weeks since prior myeloablative therapy with autologous stem cell transplantation
 - Patients who received stem cell reinfusion following non-myeloablative therapy are eligible
- More than 30 days since prior and no other concurrent investigational medications
- More than 30 days since prior and no concurrent valproic acid
- At least 2 weeks since prior radiotherapy (12 weeks for large-field radiotherapy [i.e., craniospinal, whole abdominal, total lung, > 50% marrow space])
- At least 2 weeks since prior myelosuppressive therapy or biologic therapy
- At least 7 days since prior cytokines or hematopoietic growth factors
- No concurrent hemodialysis
- No other concurrent anticancer agents, radiotherapy, chemotherapy, or immunomodulating agents
- No other concurrent medications known to prolong the QT interval
- No concurrent pentamidine prophylaxis for pneumocystis pneumonia

- No medications that interfere with MIBG uptake for 1 week before, during, and for 1 week after iobenguane I 131 therapy

Who should I contact for more information?

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