

NANT 2007-02: Bevacizumab, Cyclophosphamide, and Zoledronic Acid in Treating Patients with Recurrent or Refractory High-Risk Neuroblastoma

Rationale

Monoclonal antibodies, such as bevacizumab, 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. Drugs used in chemotherapy, such as cyclophosphamide, work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing. Zoledronic acid may stop the growth of tumor cells in bone. Giving bevacizumab together with cyclophosphamide and zoledronic acid may kill more tumor cells.

Purpose

This phase I trial is studying the side effects of giving bevacizumab together with cyclophosphamide and zoledronic acid in treating patients with recurrent or refractory high-risk neuroblastoma

Basic Study Information

Type	Status	Age Range (yrs.)	Sponsor
Interventional	Active	Up to 30 years	NANT

Objectives

Primary:

- To determine the toxicities and feasibility of bolus and metronomic cyclophosphamide when given in combination with zoledronic acid with and without bevacizumab in patients with recurrent or refractory high-risk neuroblastoma.

Secondary:

- To preliminarily evaluate the antitumor activity of this regimen in these patients within the confines of a pilot study.

Outline

This is a multicenter study. Patients receive cyclophosphamide IV over 1 hour and zoledronic acid IV over 15 minutes on day 0 and oral cyclophosphamide once daily on days 1-27 in course 1. In course 2 and all subsequent courses, patients receive bevacizumab IV over 30-90 minutes on days 0 and 14, cyclophosphamide IV over 1 hour and zoledronic acid IV over 15 minutes on day 1, and oral cyclophosphamide once daily on days 0 and 2-27. Treatment repeats every 28 days for up to 2 years* in the absence of disease progression or unacceptable toxicity.

NOTE: *Patients may receive up to 13 doses of zoledronic acid.

After completion of study treatment, patients are followed periodically.

Eligibility

Ages Eligible for Study: Up to 30 years

Disease Characteristics

- Diagnosis of high-risk neuroblastoma, verified by 1 of the following:
 - Histology
 - Demonstration of tumor cells in the bone marrow with increased urinary catecholamines
- Meets one of the following criteria:
 - Recurrent or progressive disease
 - Refractory disease (i.e., less than a partial response to front-line therapy)
 - Biopsy is not required
 - Persistent disease after achieving at least a partial response to front-line therapy (i.e., patient achieved at least a partial response to front-line therapy but still has residual disease by MIBG, CT/MRI scan, or bone marrow)
 - Biopsy of ≥ 1 residual site demonstrating viable neuroblastoma is required
- Measurable disease, as defined by ≥ 1 of the following:
 - Measurable tumor on MRI or CT scan, defined as ≥ 1 unidimensionally measurable lesion ≥ 20 mm by conventional techniques OR ≥ 10 mm by spiral CT scan
 - For patients with persistent disease, a biopsy of a soft tissue site must have demonstrated viable neuroblastoma
 - If the lesion was irradiated, biopsy must have been done ≥ 4 weeks after completion of radiotherapy
 - MIBG scan with positive uptake at ≥ 1 site
 - For patients with persistent disease, a biopsy of a MIBG-positive site must have demonstrated viable neuroblastoma
 - If the lesion was irradiated, biopsy must have been done ≥ 4 weeks after completion of radiotherapy
 - Bone marrow with tumor cells seen on routine morphology (not by neuron-specific enolase [NSE] staining alone) of bilateral aspirate and/or biopsy of 1 bone marrow sample
- No intraparenchymal brain metastasis as evidenced by screening CT scan or MRI

Patient Characteristics

- Karnofsky or Lansky performance status (PS) 50-100% (patients who are unable to walk because of paralysis or tumor pain, but who are up in a wheelchair will be considered ambulatory for the purpose of assessing PS)
- Life expectancy ≥ 4 months
- ANC $\geq 750/\text{mm}^3$

Platelet count $\geq 50,000/\text{mm}^3$ (transfusion independent, defined as no platelet transfusion for 1 week)

- Hemoglobin ≥ 8 g/dL (transfusion allowed)

PT and aPTT < 1.2 times upper limit of normal for age

- Glomerular filtration rate or creatinine clearance ≥ 70 mL/min/m² OR maximum serum creatinine based on age as follows:

- 0.8 mg/dL (for patients \leq 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)
- Hematuria \leq 1+ by urinalysis
- No more than trace protein by urinalysis OR \leq 500 mg protein by 24-hour urine collection
- Total bilirubin \leq 1.5 times normal for age
- ALT and AST $<$ 5 times normal for age
- Ionized serum calcium \geq 1.0 mmol/L (calcium supplements allowed provided serum calcium is stable)
- Ejection fraction $>$ 55% by either ECHO or radionuclide MUGA scan OR shortening fraction \geq 27% by ECHO
- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use effective contraception
- Able to comply with the safety monitoring requirements of the study
- No arterial thrombosis (including transient ischemic attack or cerebrovascular accident) within the past 6 months
- No deep venous thrombosis (including pulmonary embolism) within the past 3 months
- No history of bleeding diathesis
- No history of hemoptysis
- No history of myocardial infarction, severe or unstable angina, or peripheral vascular disease
- No NYHA class II-IV congestive heart failure
- Hypertension allowed provided it is well controlled on stable doses of medication for \geq 2 weeks prior to study enrollment
- No history of hypertensive crisis
- No history of abdominal fistula, chronic ulcer, or non-healing wound
- No documented significant trauma injury within the past 28 days
- No uncontrolled infection
- No acute active dental issues requiring intervention
- No known hypersensitivity to bevacizumab
- No other ongoing serious medical issues unless approved by the study chair prior to study enrollment

Prior Concomitant Therapy:

- Fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, radiotherapy, or surgery
- At least 3 months since prior autologous or allogeneic stem cell transplant
 - No requirement for immunosuppressants AND no active signs of graft-vs-host disease
- At least 6 weeks since prior therapeutic doses of MIBG
- At least 28 days since prior major surgical procedure (e.g., laparotomy or tumor resection)
- At least 2 weeks since prior myelosuppressive chemotherapy (4 weeks for nitrosoureas) and/or biological therapy
- At least 2 weeks since prior radiotherapy (4 weeks for radiotherapy to the site of any lesion that was biopsied to document study eligibility or to the only site of measurable disease; 6 weeks for large-field radiotherapy [i.e., total-body irradiation, craniospinal therapy, whole abdominal or total lung radiotherapy, or radiotherapy to $>$ 50% of marrow space])
- At least 7 days since prior growth factors that support hematologic quantity or function

- More than 7 days since prior minor surgical procedures (e.g., core or small incisional biopsies for limited purposes of tissue retrieval; Mediport catheter placement; or intratumoral needle biopsy for diagnostic purposes)
- No other concurrent anticancer agents, including chemotherapy, radiotherapy, immunomodulating agents, or investigational agents
- No concurrent full-dose anticoagulants
- Concurrent low-dose aspirin (≤ 325 mg/day) allowed for patients at a higher risk for arterial thromboembolic disease
- Concurrent corticosteroids allowed provided the patient has been a stable dose for ≥ 2 weeks or is on a tapering schedule
- No concurrent teeth extractions

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