ANBL1021: Feasibility/Phase II Study of hu14.18-IL2 Immunocytokine + GM-CSF and Isotretinoin in Patients with Relapsed or Refractory Neuroblastoma

Basic Study Information

Study Type: Interventional

Study Design: Masking: Open Label

Primary Purpose: Treatment

Purpose

This phase II trial is studying how well biological therapy works when given together with sargramostim and isotretinoin in treating patients with relapsed or refractory neuroblastoma.

Objectives

Primary

- To evaluate the safety and tolerability of sargramostim (GM-CSF) and isotretinoin given in combination with hu14.18-IL2 fusion protein (hu14.18-IL-2), as a test of feasibility for a future Phase III study.
- To evaluate the anti-tumor activity of hu14.18-IL2 given in combination with GM-CSF and isotretinoin in patients with recurrent or refractory neuroblastoma with disease measurable by standard radiographic criteria (stratum-1).
- To evaluate the anti-tumor activity of hu14.18-IL2 given in combination with GM-CSF and isotretinoin in patients with recurrent or refractory neuroblastoma evaluable only by meta-iodobenzyl guanidine I 123 (MIBG) scintigraphy and/or bone marrow histology (stratum-2).

Secondary

- To describe the disease burden of stratum-2 patients by semi-quantitative assessment of bone marrow and MIBG scintigraphy and determine whether there is an association between lower disease burden and response to hu14.18-IL2.
- To assess molecular parameters of response (RT-PCR) for patients meeting CR criteria.
- To evaluate the immunologic activation induced in vivo by hu14.18-IL2.
- To determine the induction of anti-hu14.18-IL2 antibody by treatment with hu14.18-IL2.
- To test for associations between tumor response versus immune activation and anti-hu14.18-IL2 activity, and between measurements of toxicity versus immune activation and anti-hu14.18-IL2 activity.

Outline

This is a multicenter study. Patients are stratified according to measurable disease (disease measurable by standard radiographic criteria [stratum-1] vs disease evaluable only by 123I-MIBG and/or bone marrow histology [stratum-2]).

Patients receive sargramostim subcutaneously (SC [preferred]) or IV over 2 hours on days 1-2 and 8-14, hu14.18-IL2 fusion protein IV over 4 hours on days 4-6, and isotretinoin orally twice daily on days 11-24. Treatment repeats every 28 days for 4-10 courses in the absence of disease progression or unacceptable toxicity. Patients in stratum-1 who achieve stable disease (SD) after course 4 are removed from protocol therapy. Patients in stratum-2 who achieve SD after course 4 receive 2 additional courses of study treatment.

Patients may undergo blood and bone marrow sample collection periodically for correlative studies.

After completion of study therapy, patients are followed up every 3 months for 1 year, every 6 months for 2 years, and then yearly for 2 years.

Ages Eligible for Study: 1 Year to 30 Years

Entry Criteria

Disease Characteristics:

- Patients must have had histologic verification of neuroblastoma and/or demonstration of tumor cells in the bone marrow with increased urinary catecholamines at the time of initial diagnosis
- Patients must have resistant/refractory or recurrent neuroblastoma
- Tumor imaging and bone marrow evaluation for histologic analysis of marrow tumor cell quantity must be obtained within 3 weeks (21 days) prior to enrollment onto study and patients must have one of the following:
    - Measurable tumor on MRI, CT scan, or x-ray defined as minimum of 20 mm in at least one dimension
        - For patients who are in first response (i.e., those patients with persistent sites of tumor after frontline therapy, but who have never relapsed), a biopsy of a lesion or bone marrow must demonstrate viable neuroblastoma following completion of therapy
        - If the lesion was irradiated, the biopsy must be done at least 4 weeks after radiation is completed
    - Meta-iodobenzyl guanidine I 123 (MIBG) scan with positive uptake at minimum of one site
        - For patients in first response, a biopsy of site must demonstrate viable tumor
        - If lesion was radiated, biopsy must be done at least 4 weeks after radiation completed
    - Bone marrow with tumor cells seen on routine morphology (not by neuron specific enolase [NSE] staining only) of bilateral aspirate and/or biopsy on one bone marrow sample
- No patients with symptomatic pleural effusions or ascites (requiring constant or intermittent drainage)
- Patients with a history of CNS disease must have no clinical or radiological evidence of CNS disease at the time of protocol enrollment

Patient Characteristics:

- Performance status (PS) 0-2
    - Karnofsky PS 50-100% for patients > 16 years of age and Lansky PS 50-100% for patients ≤ 16 years of age
- Patients must have a life expectancy of ≥ 8 weeks
- Absolute phagocyte count (APC) ≥ 1,000/μL
- Platelet count ≥ 20,000/μL*
- Hemoglobin ≥ 8 g/dL*
- Creatinine clearance or radioisotope GFR ≥ 70 mL/min OR serum creatinine based on age/gender as follows:
    - 0.4 mg/dL (1 month to < 6 months of age)
    - 0.5 mg/dL (6 months to < 1 years of age)
    - 0.6 mg/dL (1 to < 2 years of age)
    - 0.8 mg/dL (2 to < 6 years of age)
    - 1.0 mg/dL (6 to < 10 years of age)
    - 1.2 mg/dL (10 to < 13 years of age)
    - 1.5 mg/dL (male) or 1.4 mg/dL (female) (13 to < 16 years of age)
    - 1.7 mg/dL (male) or 1.4 mg/dL (female) (≥ 16 years of age)
- Not pregnant or nursing
- Negative pregnancy test

- Patients of childbearing potential must agree to use an effective birth control method
- Total bilirubin ≤ 1.5 times upper limit of normal (ULN)
- ALT ≤ 1.5 times ULN
- Shortening fraction ≥ 27% by echocardiogram OR ejection fraction ≥ 55% by gated radionuclide study
- QTC interval < 450 msec
- Patients must have normal respiratory function defined as no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry > 94% on room air
    - If pulmonary function tests (PFTs) are performed, the FEV1/FVC must be greater than 60%
- Patients with seizure disorders may be enrolled if on anti-convulsants and well-controlled
- CNS toxicity ≤ grade 2
- Patients with symptoms of congestive heart failure or uncontrolled cardiac rhythm disturbance are not eligible
- Patients with prior history of ventilator support related to lung injury (lung injury such as pneumonia, hemorrhagic pneumonitis, capillary leakage) are excluded
- Patients with significant serious intercurrent illnesses (any other ongoing serious medical problem unrelated to cancer or its treatment) that is not covered by the detailed exclusion criteria and which is expected to interfere with the action of hu14.18-IL2 or to significantly increase the severity of the toxicities experienced from hu14.18-IL2 treatment are not eligible.

NOTE: *Transfusions are permitted if known history of bone marrow involvement with tumor.

Prior/Concurrent Therapy

- Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study
- Must not have received myelosuppressive chemotherapy within 3 weeks of entry onto this study (4 weeks if prior nitrosourea)
- At least 7 days since the completion of therapy with a non-myelosuppressive biologic agent
- At least 2 weeks since prior local palliative radiotherapy (RT) (small port)
    - Concurrent radiotherapy to localized painful lesions acceptable, provided ≥ 1 measurable/MIBG-evaluable lesion is not irradiated
- At least 6 months since prior craniospinal RT or ≥ 50% of RT of the pelvis
- At least 6 weeks since other prior substantial bone marrow RT
- More than 56 days since prior autologous bone marrow or stem cell transplants
    - Patients who have received an allogenic stem cell transplant are excluded
- Patients who have previously received in vivo anti-GD2 monoclonal antibodies for biologic therapy or for tumor imaging are eligible unless they have had progressive disease while receiving prior anti-GD2 therapy
- Patients who have received autologous marrow infusions or autologous stem cell infusions using monoclonal antibody linked to beads to purge specimens, but no other form of anti-GD2 monoclonal antibody, are eligible
- Must not have received growth factor(s) within 1 week of entry onto this study
- Patients who require or are likely to require corticosteroid or other immunosuppressive drugs for intercurrent disease (any other significant medical problem related to or independent from the neuroblastoma or its treatment) while tentatively scheduled to be receiving treatment on this study are ineligible
    - The only exception is for patients known to require 2 mg/kg or less of hydrocortisone (or an equivalent dose of an alternative corticosteroid) as premedication for blood product transfusion in order to avoid allergic transfusion reactions

- Patients who have had major surgery (i.e., laparotomy or thoracotomy) within the past 2 weeks are not eligible
- Patients with organ allografts (including bone marrow or stem cell) are not eligible
- No other concurrent anticancer therapy
- No other concurrent cytokines or growth factors

For more information contact:

Cincinnati Children's Hospital Medical Center
Division of Hematology/Oncology
3333 Burnet Ave., Cincinnati, OH 45229-3039
Phone: 513-636-2799
cancer@cchmc.org