NANT 99-02: Modulation of Intensive Melphalan (L-PAM) by Buthionine Sulfoximine (BSO) with Autologous Stem Cell Support for Recurrent High-Risk Neuroblastoma (A Phase I Study)

Basic Study Information

Type of Trial	Status of Trial	Age Range (yrs.)	Sponsor of Trial	Protocol ID
Treatment	Active	> 9 months ≤ 30 years	NANT	N99-02

Outline

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

Patients receive buthionine sulfoximine IV as a bolus over 30 minutes followed by a 72-hour continuous infusion beginning on day -4; melphalan IV over 15 minutes on days -3 and -2; autologous peripheral blood stem cells or bone marrow IV over 15-30 minutes on day 0; and filgrastim (G-CSF) subcutaneously or IV once daily beginning on day 0 and continuing until blood counts recover.

Cohorts of 3-6 patients receive escalating doses of melphalan until the maximum tolerated dose (MTD) is determined. The MTD is defined as the dose preceding that at which 2 of 3 or 2 of 6 patients experience dose-limiting toxicity.

Patients are followed at 84 days and then 2 months later if there is a complete and/or partial response. Patients who continue therapy on other protocols are followed before starting the new therapy. All patients are followed for life for any delayed toxic effects to protocol therapy and secondary malignancies.

Objectives

1. Determine the maximum tolerated dose of melphalan when combined with buthionine sulfoximine and followed by autologous bone marrow or peripheral blood stem cell support in children with recurrent high-risk neuroblastoma.
2. Assess the toxic effects of this regimen in these patients.
3. Determine the pharmacokinetics of this regimen in these patients.
4. Determine the response rate of patients treated with this regimen.

Projected Accrual

A total of 30 patients will be accrued for this study within 2-3 years

Entry Criteria

Disease Characteristics:

- Diagnosis of high-risk neuroblastoma confirmed by histology and/or tumor cells in bone marrow with elevated urinary catecholamine metabolites

- Meets 1 of the following response status criteria:
  - Current or previous progressive disease
  - Mixed or no response following completion of minimum of 4 courses of induction therapy
- Meets 1 of the following criteria:
  - Measurable disease, defined as ≥ 1 unidimensionally measurable lesion ≥ 20 mm by conventional techniques OR ≥ 10 mm by spiral CT scan
  - Metaiodobenzylguanidine (MIBG) scan with uptake at a minimum of one site
  - Bone marrow disease documented by standard morphology of bilateral bone marrow aspirate and biopsy specimens
- Documentation by positive immunocytology is not sufficient
  - Biopsy of a lesion seen on bone scan that is non-avid for MIBG and that demonstrates viable neuroblastoma
- Meets 1 of the following criteria for harvested autologous stem cells:
  - Availability of at least 1.5 x 106 CD34-positive unpurged autologous peripheral blood stem cells per kg of body weight*
  - Availability of at least 1.0 x 106 viable CD34-positive purged autologous peripheral blood stem cells per kg of body weight*
- A backup source of stem cells is required if there are < 1.5 x 106 CD34-positive viable cells/kg available for infusion
  - Availability of at least 1 x 108 purged autologous mononuclear bone marrow cells per kg of body weight* NOTE: *Product to be infused must have 0 tumor cells by immunocytology
- No history of intraparenchymal brain lesion
- No concurrent intraparenchymal brain lesion or meningeal/parameningeal soft tissue mass extending directly into the cranial cavity by CT, MRI, or metaiodobenzylguanidine scan

Prior/Concurrent Therapy:

Biologic therapy

- See Disease Characteristics
- At least 3 weeks since prior biologic therapy and recovered

Chemotherapy

- At least 3 weeks since prior chemotherapy (6 weeks for mitomycin or nitrosoureas) and recovered
- No other concurrent anticancer chemotherapy

Endocrine Therapy

- Not specified

Radiotherapy

- Recovered from prior radiotherapy
- Prior diagnostic radiotherapy allowed
- More than 6 months since prior radiotherapy to mantle and Y ports
- More than 3 months since prior therapeutic metaiodobenzylguanidine (131I-MIBG) and no more than 20 mCl/kg total dose received

- At least 2 weeks since prior radiotherapy to all other sites
- More than 6 months since prior radiotherapy to kidneys, liver, heart, skull, or face
  - No more than 25% of the liver can have received > 1800 cGy
  - No more than 20% of one of the kidneys can have received > 1200 cGy
  - No more than a 10 cc volume of the brain can have received > 1000 cGy
- No prior total body irradiation
- No prior total cranial or craniospinal radiotherapy
- No concurrent radiotherapy

Surgery

- Not specified

Other

- Recovered from any prior therapy
- At least 7 days since prior antibiotics, antifungals, or antivirals
- No acetaminophen or cephalosporin antibiotics for at least 7 days before, during, and until at least 2 weeks after buthionine sulfoximine infusion
- No prophylactic antimicrobials (i.e., nystatin or sulfamethoxazole/trimethoprim) for at least 7 days before, during, and until at least 7 days after buthionine sulfoximine infusion
- No concurrent antiretroviral medications for HIV-positive patients

Patient Characteristics:

Age

- Over 9 months to 30 years

Performance status

- ECOG or Zubrod 0-1

Life expectancy

- At least 2 months

Hematopoietic

- Absolute neutrophil count at least 500/mm3
- Platelet count at least 20,000/mm3 (transfusion allowed)
- Hemoglobin at least 10 g/dL (transfusion allowed)

Hepatic

- Bilirubin normal
- AST and ALT no greater than 2.5 times normal
- No active hepatitis if HIV positive

Renal

- Glomerular filtration rate or creatinine clearance > 100 mL/min
- Creatinine < 1.5 times normal

Cardiovascular

- Ejection fraction at least 55% by echocardiogram or MUGA scan

OR

- Fractional shortening at least 30% by echocardiogram

Pulmonary

- No dyspnea at rest or exercise intolerance
- No active pneumonia if HIV positive

Neurologic

- No grade 1 or greater neurologic function abnormality except grade 1 irritability, headache, dizziness, insomnia, or somnolence (if due to narcotic analgesics)
- No history of seizures

Other

- No other active health problems if HIV positive
- No concurrent neoplastic or nonneoplastic disease of any major organ system that would preclude study participation
- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use effective contraception