

00-C-0092: A Randomized Trial of Filgrastim-SD/01 vs. Filgrastim in Newly Diagnosed Children and Young Adults with Sarcoma Treated with Dose-Intensive Chemotherapy

Filgrastim -SD/01, which is produced by PEGylation of the amino-terminus of Filgrastim, is a sustained duration form of granulocyte colony-stimulating factor. The purpose of this randomized open labeled trial is to compare the tolerance, toxicity and therapeutic effects of Filgrastim-SD01 given as a single injection after standard chemotherapy to daily subcutaneous Filgrastim in patients with newly diagnosed sarcoma. The pharmacokinetics of Filgrastim -SD/01 will be compared to the pharmacokinetics of Filgrastim. This trial will also be a platform for performing biological studies of these tumors and for detailed cardiac studies.

ELIGIBILITY CRITERIA:

Age: <25years of age

Histological Diagnosis: Newly diagnosed histologically proven:

- Ewing's sarcoma family of tumors, including peripheral neuroectodermal tumors
- Alveolar rhabdomyosarcoma
- Stage 3 or 4 embryonal rhabdomyosarcoma
- Malignant peripheral nerve sheath tumor that is unresectable, incompletely resected with bulk residual disease or metastatic
- Synovial cell sarcoma that is unresectable, incompletely resected with bulk residual disease, or metastatic.

Cardiac Function: Normal cardiac function (ejection fraction by MUGA or ECHO that is within the institutional normal range).

Renal Function: Normal serum creatinine for age (see Table below) or creatinine clearance >60 ml/min/1.73 m².

Age (Years)	Maximum Serum Creatinine (mg/dl)
≤ 5	0.8
5 < age ≤ 10	1.0
10 < age ≤ 15	1.2
> 15	1.5

Hepatic Function: SGPT < 5 x the upper limit of normal and bilirubin <2.5 x the upper limit of normal

Hematologic Function: Normal hematologic function (absolute neutrophil count > 1500/ μ L, HGB > 9.0 g/dl and PLT > 100,000/ μ L)

EXCLUSION CRITERIA:

- Previous chemotherapy or radiotherapy
- Pregnant or breast feeding females
- Histological evidence of tumor infiltration of bone marrow
- Stage 1 or 2 embryonal rhabdomyosarcoma

PRETREATMENT EVALUATION:

- History and Physical: documentation of signs and symptoms, measurable disease, height, weight, & BSA
- Labs: CBC/diff, PT/PTT, fibrinogen, ESR, LDH, Na, K, Cl, CO₂, BUN, serum creatinine, serum glucose, calcium, magnesium, phosphorus, alkaline phosphatase, SGOT/SGPT, total bilirubin, urinalysis, urine pregnancy test in post-menarchal females, serum cTnT (serum Troponin T) level
- Imaging Studies: plain x-ray of chest and primary site; CT chest; CT and MRI of primary site; bone scan
- Cardiac Evaluation: MUGA or Echo required and Cardiac MRI when possible
- Marrow Evaluation: bilateral bone marrow aspiration and biopsy for patients with Ewing's sarcoma, alveolar and embryonal rhabdomyosarcoma

- Tumor Histology: review of outside slides or tumor blocks if available otherwise a biopsy will be performed
- Prior to NIH screening please send: physician summary, lab work, scans, pathology slides/blocks and report

GENERAL TREATMENT PLAN:

- Standard chemotherapy will include vincristine, doxorubicin, cyclophosphamide alternating with etoposide and ifosfamide
- Patients will be randomized to receive either Filgrastim or Filgrastim-SD/01
- Filgrastim dose is $5\mu\text{g/kg/dose}$ SQ daily starting 24-36 hrs after day 2 dose of cyclophosphamide or day 5 of ifosfamide and continuing until post-nadir neutrophil count $>10,000/\mu\text{L}$
- Filgrastim-SD/01 dose is $100\mu\text{g/kg/dose}$ SQ x 1 dose 24-36 hours after day 2 dose of cyclophosphamide or day 5 of ifosfamide
- In general, local control will commence after cycle 5 and may include surgical resection or radiation therapy

PHARMACOKINETICS:

- Serum samples for Filgrastim and Filgrastim-SD/01 will be obtained during cycle 1 of chemotherapy ONLY. Samples should be obtained prior to the first dose and then 1, 2, 4, 6, 8, 24, and 28 hrs after the day 1 dose of Filgrastim or Filgrastim-SD/01
- Filgrastim trough samples should be obtained on days 4, 6, 8, and 10 and 4 hours after the day 10 dose
- Filgrastim-SD/01 samples should be obtained on days 4, 6, 8, 10, and 21

CORRELATIVE STUDIES:

- Minimal Residual Disease: Ewing's and alveolar rhabdomyosarcoma pts only. 10 ml heparinized blood and apheresis sample (not to exceed one blood volume) at specified time points. Simultaneous peripheral blood samples for PCR will be obtained (10 ml heparinized tube) with bone marrows.
- Tumor Biology: tumor tissue will be processed for development of cell lines & murine xenotransplant models
- Cardiac MRI and Serum Troponin T: cardiac MRI and cTnT levels should be obtained at specified time points.
- Neutrophil Function Studies: will be performed using PMNs & plasma., organisms, superoxide anion production assay, measurement of circulating cytokines and expression of m-RNA components of NADPH oxidase.
- CD34-Positive Stem Cell Levels: 10 ml of heparinized blood for quantification of CD34 positive stem cells

ACCRUAL:

Open to accrual. Patients meeting eligibility criteria can be referred to the Pediatric Oncology Branch NCI or Children's Hospital and Regional Center in Seattle for evaluation and treatment