

## SARC 006: Phase II Trial of Chemotherapy in Sporadic and Neurofibromatosis Type 1 Associated High Grade Malignant Peripheral Nerve Sheath Tumors

Type	Status	Age Range (yrs.)	Sponsor
Interventional	Active	not defined	CCHMC

### Rationale

Drugs used in chemotherapy, such as doxorubicin, ifosfamide, and etoposide, work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing. Radiation therapy uses high-energy x-rays to kill tumor cells. Giving combination chemotherapy with or without radiation therapy before surgery may make the tumor smaller and reduce the amount of normal tissue that needs to be removed. Giving combination chemotherapy after surgery may kill any tumor cells that remain after surgery.

### Purpose

This phase II trial is studying how well combination chemotherapy works in treating patients with stage III or stage IV malignant peripheral nerve sheath tumors.

### Objectives

#### Primary

- Determine the clinical response rate (complete and partial) in patients with sporadic or neurofibromatosis type 1 (NF1)-associated high-grade stage III or IV malignant peripheral nerve sheath tumors (MPNSTs) after treatment with 4 courses of chemotherapy comprising doxorubicin hydrochloride and ifosfamide (IA) followed by etoposide and ifosfamide (IE)

#### Secondary

- Evaluate the utility of fludeoxyglucose F18 positron emission tomography (<sup>18</sup>F-FDG-PET) and automated MRI volumetric tumor analysis as tools to assess response to treatment.
- Correlate response evaluation by 2-dimensional WHO criteria, 1-dimensional RECIST criteria, <sup>18</sup>F-FDG-PET, and volumetric MRI with percent necrosis in tumor specimens from patients who undergo surgery for local control after chemotherapy.
- Evaluate the response of plexiform neurofibroma(s) (if present) to chemotherapy using WHO criteria and automated volumetric MRI analysis.
- Evaluate the molecular biology of sporadic and NF1-associated MPNSTs by performing a detailed pathologic analysis of tumor samples with the goal to analyze if markers can be identified that predict for response to chemotherapy or outcome.

- Construct a tissue microarray from submitted tumor samples, that will be used in the future to identify novel targets for treatment of MPNSTs.
- Assess if a serum biomarker can be identified, that predicts for the presence of a MPNST versus benign plexiform neurofibroma.
- Increase the knowledge of the epidemiology and clinical presentation of NF1-associated MPNSTs.

## Outline

This is a multicenter study. Patients are stratified according to type of malignant peripheral nerve sheath tumor (MPNST) (sporadic MPNST vs neurofibromatosis type 1 [NF1]-associated MPNST). Patients receive 1 of 2 treatment regimens depending on the location of the MPNST and tumor response to chemotherapy.

- Chemotherapy and local control by radiotherapy and surgery: Patients receive doxorubicin hydrochloride and ifosfamide (IA) chemotherapy comprising doxorubicin hydrochloride IV over 15 minutes on days 1 and 2 and ifosfamide IV over 1 hour on days 1-5. Treatment repeats every 21 days for 2 courses in the absence of unacceptable toxicity. Patients then receive etoposide and ifosfamide (IE) chemotherapy comprising etoposide IV over 1 hour and ifosfamide IV over 1 hour on days 1-5. Treatment repeats every 21 days for 2 courses in the absence of disease progression or unacceptable toxicity. Patients also receive filgrastim (G-CSF) subcutaneously (SC) after each chemotherapy course beginning on day 6 or 7 and continuing until blood counts recover or pegfilgrastim SC once on day 6 or 7.

After recovery from chemotherapy, patients undergo radiotherapy and receive 2 more courses of IE during radiotherapy followed by 2 more courses of IA after completion of radiotherapy. Some patients may then undergo surgery.

- Chemotherapy and local control by surgery: Patients receive 2 courses of IA followed by 2 courses of IE as above. After recovery from chemotherapy, patients undergo surgery. After recovery from surgery, patients receive 2 more courses of IA followed by 2 more courses of IE in the absence of disease progression or unacceptable toxicity. After completion of study treatment, patients are followed periodically for up to 5 years.

## Disease Characteristics

- Newly diagnosed sporadic or neurofibromatosis type 1 (NF1)-associated high-grade malignant peripheral nerve sheath tumors (MPNSTs)
  - Stage III or stage IV (metastatic) disease
- Measurable disease, defined as at least 1 tumor that is measurable in 2 dimensions on CT scan or MRI

## Patient Characteristics

- Ejection fraction normal by echocardiogram or MUGA
- Serum creatinine normal for age OR creatinine clearance > 60 mL/min
- SGPT < 5 times upper limit of normal (ULN)
- Bilirubin < 2.5 times ULN
- Absolute neutrophil count  $\geq 1,500/\text{mm}^3$ \*
- Hemoglobin  $\geq 9.0$  g/dL\*
- Platelet count  $\geq 100,000/\text{mm}^3$ \*

- ECOG performance status 0-2
- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use effective contraception during and for 6 months after completion of study treatment

\*Note: Unsupported

## Prior Concurrent Therapy:

- No prior chemotherapy for MPNST
- Prior surgical resection of MPNST allowed provided residual or recurrent measurable disease is present
- Recovered from toxic effects of all prior therapy
- At least 3 weeks since prior chemotherapy or biologic therapy for treatment of a plexiform neurofibroma, optical pathway tumor, or other NF1-associated tumor (in patients with NF1)
- No prior doxorubicin, ifosfamide, or etoposide
- At least 6 weeks since prior radiotherapy for treatment of a plexiform neurofibroma, optical pathway tumor, or other NF1-associated tumor (in patients with NF1)
- At least 4 weeks since prior radiotherapy to the area involved by MPNST
- No other concurrent growth factors (e.g., sargramostim [GM-CSF] or interleukin-11)
  - Concurrent epoetin alfa allowed

## Who should I contact for more information?

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