5.0 TREATMENT PLAN AND DOSE MODIFICATIONS

5.1 General Plan of Therapy

Treatment will occur in two phases: Induction and Continuation, with 14 cycles of chemotherapy in all. Induction consists of the first twelve weeks (four cycles on Regimen A and six cycles on Regimen B). The cycles alternate between vincristine-doxorubicin-cyclophosphamide-MESNA and ifosfamide-etoposide-MESNA. G-CSF (Filgrastim) is given between chemotherapy doses. Regimens A and B differ only by the timing of the chemotherapy. Local control (surgery, radiation, or a combination) will begin on Week 13 in both regimens, which will be after four cycles of chemotherapy in Regimen A and six cycles of chemotherapy in Regimen B.

Week	Regimen A_1, Surgery only	Regimen A_2, Radiation only	Regimen A_3, Surgery then Radiation	Regimen B_1, Surgery only	Regimen B_2, Radiation only	Regimen B_3, Surgery then Radiation
1	Cycle 1 (VDC)	Cycle 1 (VDC)	Cycle 1 (VDC)	Cycle 1 (VDC)	Cycle 1 (VDC)	Cycle 1 (VDC)
2						
3				Cycle 2 (IE)	Cycle 2 (IE)	Cycle 2 (IE)
4	Cycle 2 (IE)	Cycle 2 (IE)	Cycle 2 (IE)			
5				Cycle 3 (VDC)	Cycle 3 (VDC)	Cycle 3 (VDC)
6						
7	Cycle 3 (VDC)	Cycle 3 (VDC)	Cycle 3 (VDC)	Cycle 4 (IE)	Cycle 4 (IE)	Cycle 4 (IE)
8						
9				Cycle 5 (VDC)	Cycle 5 (VDC)	Cycle 5 (VDC)
10	Cycle 4 (IE)	Cycle 4 (IE)	Cycle 4 (IE)			
11				Cycle 6 (IE)	Cycle 6 (IE)	Cycle 6 (IE)
12						
13	SURGERY	Cycle 5 (VDC) start RT	SURGERY	SURGERY	Cycle 7 (VDC) start RT	SURGERY
14						
15	Cycle 5 (VDC)		Cycle 5 (VDC) start RT	Cycle 7 (VDC)	Cycle 8 (IE)	Cycle 7 (VDC) start RT
16		Cycle 6 (IE)				
17				Cycle 8 (IE)	Cycle 9 (VC)	Cycle 8 (IE)
18	Cycle 6 (IE)		Cycle 6 (IE)			
19		Cycle 7 (VC)		Cycle 9 (VDC)	Cycle 10 (IE)	Cycle 9 (VC)
20						
21	Cycle 7 (VDC)		Cycle 7 (VC)	Cycle 10 (IE)	Cycle 11 (VC)	Cycle 10 (IE)
22		Cycle 8 (IE)				
23				Cycle 11 (VC)	Cycle 12 (IE)	Cycle 11 (VC)
24	Cycle 8 (IE)		Cycle 8 (IE)			
25		Cycle 9 (VDC)		Cycle 12 (IE)	Cycle 13 (VDC)	Cycle 12 (IE)
26						
27	Cycle 9 (VDC)		Cycle 9 (VDC)	Cycle 13 (VC)	Cycle 14 (IE)	Cycle 13 (VDC)
28		Cycle 10 (IE)				
29				Cycle 14 (IE)		Cycle 14 (IE)
30	Cycle 10 (IE)		Cycle 10 (IE)			
31		Cycle 11 (VDC)				
32						
33	Cycle 11 (VC)		Cycle 11 (VDC)			
34		Cycle 12 (IE)				
35						
36	Cycle 12 (IE)		Cycle 12 (IE)			
37		Cycle 13 (VC)				
38						
39	Cycle 13 (VC)		Cycle 13 (VC)			
40		Cycle 14 (IE)				
41						
42	Cycle 14 (IE)		Cycle 14 (IE)			
43						

IE = Ifosfamide – Etoposide - MESNA
VDC = Vincristine – Doxorubicin – Cyclophosphamide - MESNA
VC = Vincristine - Cyclophosphamide - MESNA

Cycles 1: The first cycle will consist of the vincristine, doxorubicin, and cyclophosphamide. All three drugs will be given over the first 3 days of treatment.

Recovery: Following this treatment there is a recovery period that will continue for either 2 weeks (New Regimen) or 3 weeks (Standard Regimen) from the first day of treatment. During the recovery period your child will receive the G-CSF until blood cells recover from chemotherapy.

Cycle 2: After the recovery period, your child will be treated with the second cycle, which will consist of ifosfamide and etoposide. The ifosfamide and etoposide will be given for 5 days. After the ifosfamide and etoposide, there will be another recovery period for 2 weeks (New Regimen) or 3 weeks (Standard Regimen) from the first day of the cycle.

The treatment will continue like this, alternating between the two sets of drugs with recovery periods in between. Your child will receive a total of 14 cycles of chemotherapy.

After the first 6 cycles of the New Regimen, or after the first 4 cycles of the Standard Regimen, the tumor will be treated with radiation or surgery, or both. Your child's doctors will discuss these procedures with you later, and obtain your consent separately. The remaining alternating cycles and recovery periods will continue after the radiation/surgery.

New Regimen (2-week intervals)

Cycle 1: **Vincristine, Doxorubicin, and Cyclophosphamide** [1,2]
Two-week Recovery[3]
Cycle 2: **Ifosfamide and Etoposide** [1,2]

Two-week Recovery
Cycle 3: **Vincristine, Doxorubicin, and Cyclophosphamide**
Two-week Recovery
Cycle 4: **Ifosfamide and Etoposide**[1,2]

Two-week Recovery

Cycle 5: **Vincristine, Doxorubicin, and Cyclophosphamide**
Two-week Recovery
Cycle 6: **Ifosfamide and Etoposide**

↓

Surgery and/or Radiation

↓

Repeat 8 more cycles of chemotherapy[4]

Standard Regimen (3-week intervals)

Cycle 1: **Vincristine, Doxorubicin, and Cyclophosphamide** [1,2]
Three-week Recovery[3]
Cycle 2: **Ifosfamide and Etoposide** [1,2]

Three-week Recovery
Cycle 3: **Vincristine, Doxorubicin, and Cyclophosphamide**
Three-week Recovery
Cycle 4: **Ifosfamide and Etoposide**[1,2]

↓

Surgery and/or Radiation

↓

Repeat 10 more cycles of chemotherapy[4]

5.1.1 Methods of Chemotherapy Administration

In the interest of improving the safety of chemotherapy administration, several institutions have established standard methods that override the methods outlined in most protocols. The COG Pharmacy committee is also developing chemotherapy administration standards for the commonly used agents. The instructions below conform to the COG chemotherapy standards for all agents except doxorubicin (for which no standard is available yet) and the listed recommendations are abstracted from the standards. **These instructions should be followed except when they vary from institutional chemotherapy standards developed for purposes of promoting medication safety, and approved by the institutional Therapeutic Standards Committee or equivalent body.**

5.2 Vincristine-Doxorubicin-Cyclophosphamide - MESNA (see schedules in Section 5.1)

5.2.1 Vincristine

Vincristine 2 mg/m^2 IV push, on Day 1. Maximum dose 2 mg.

For children < 1 year treat with 50% doses calculated on a m^2 basis. If tolerated (no delay in administration of the next cycle due to delayed count recovery or delayed resolution of other toxicities and no serious toxicities), consider increasing to 75% and then to 100% of the calculated full dose.

5.2.2 Doxorubicin

Doxorubicin 75 mg/m^2/course continuous IV infusion over 48 hours, beginning Day 1.

Note: The total doxorubicin dose **per cycle** is 75 mg/m^2, which will be given as 37.5 mg/m^2/day x 2 days. Doxorubicin may be given differently in order to comply with institutional standards established for medication safety purposes IF 1) the approval of the Study Chair is obtained and 2) the variant method of administration is noted on the Roadmap.

For children < 1 year treat with 50% doses calculated on a m^2 basis. If tolerated (no delay in administration of the next cycle due to delayed count recovery or delayed resolution of other toxicities and no serious toxicities), consider increasing to 75% and then to 100% of the calculated full dose.

Since the total dose of doxorubicin in this protocol is 375 mg/m^2, two cycles of vincristine and cyclophosphamide are administered without doxorubicin. These cycles occurs toward the end of therapy for patients not receiving radiation, and during or shortly after radiation therapy for irradiated patients. (See schedules in Section 5.1). Doxorubicin should not be given during radiation therapy, except at the beginning of radiation therapy (cycle 5 on Regimen A_2 and A_3 or cycle 7 on Regimen B_2 and B_3). (See Section 14.5.1) (See Section 5.5.3.2 for information on substituting Dactinomycin for Doxorubicin in cases of cardiac abnormality).

Note regarding dexrazoxane (ZineCard): It has not been established that dexrazoxane provides cardiac protection without diminishing the anti-tumor efficacy of anthracyclines. The manufacturer suggests starting dexrazoxane only after a 300 mg/m^2 cumulative dose is achieved. Since this protocol uses a total dose of only 375 mg/m^2, dexrazoxane use is not permitted except under special circumstances that must be discussed with the Study Chair.

5.2.3 Cyclophosphamide

Cyclophosphamide 1200 mg/m^2 IV infusion over 1 hour with MESNA uroprotection, on Day 1.

For children < 1 year treat with 50% doses calculated on a m^2 basis. If tolerated (no delay in administration of the next cycle due to delayed count recovery or delayed resolution of other toxicities and no serious toxicities), consider increasing to 75% and then to 100% of the calculated full dose.

Recommendations:

Hydration: 3000 mL/m^2/day (125 mL/m^2/hour) using fluid containing at least 0.45% saline; (for adult-sized adolescents use 3000 mL/day as the minimum total fluid volume)

Urine Specific Gravity < 1,010 prior to start of chemotherapy

Urine output: Before infusion > 100 mL/m^2/hour (or 3 mL/kg/hour)

After infusion > 65 mL/m^2/hour (or 2 mL/kg/hour)

Monitor for hematuria: at least every 8 hours

Monitor serum electrolytes

Dilution: Administer as undiluted drug (20 mg/mL) or further dilute in a standard volume of 50, 100, or 250 mL with compatible IV fluid

Infusion time for doses ≤ 1800 mg/m^2/day should be one hour

5.2.4 MESNA

The use of MESNA with cyclophosphamide and ifosfamide is required. In the past, MESNA was held during radiation therapy. There are no data to suggest MESNA is a radioprotector. MESNA will therefore not be held during radiation therapy. The total daily MESNA dose is equal to at least 60% of the daily cyclophosphamide or ifosfamide dose (for example, 20% of the cyclophosphamide or ifosfamide dose in the bag with the drug and 2 boluses of the same dose at hours 4 and 8 after the infusion), or by continuous infusion of the 60% dose. MESNA continuous infusion should be started at the same time as the cyclophosphamide/ifosfamide and be completed no sooner than 8 hours after the end of the cyclophosphamide or ifosfamide infusion (e.g. with a one hour cyclophosphamide infusion, the MESNA continuous infusion would be at least 9 hours). The oral dose of MESNA is 2x the IV dose. Patients able to tolerate oral MESNA may receive the final dose by mouth at 40% of the oxazaphosphorine (cyclophosphamide or ifosfamide) dose.

5.2.5 G-CSF (Filgrastim)

G-CSF (Filgrastim) 5 micrograms/kg/day **subcutaneously** beginning a full 24 hours after the last dose of chemotherapy (which may mean giving the dose in the evening), and continuing until the absolute neutrophil count is 750/μL or greater.

Note regarding GM-CSF (Sargramostim): In an NCI pilot study, GM-CSF did not permit interval compression of chemotherapy (24). **Do not substitute GM-CSF for G-CSF (Filgrastim) in this study.**

5.3 Ifosfamide-Etoposide-MESNA (see schedules in Section 5.1)

5.3.1 Ifosfamide

Ifosfamide 1800 mg/m^2/day IV infusion over 1 hour, Days 1-5 of each cycle. (9,000 mg/m^2 max total dose). Prehydrate for 6 hours, 1,000 ml/m^2.

For children < 1 year treat with 50% doses calculated on a m^2 basis. If tolerated (no delay in administration of the next cycle due to delayed count recovery or delayed resolution of other toxicities and no serious toxicities), consider increasing to 75% and then to 100% of the calculated full dose.

Recommendations:
Hydration: 3000ml/m^2/day (125ml/ m^2/hour) using fluid containing 0.45% or 0.9% saline; (for adult-sized adolescents use 3000mL per day as the minimum total fluid volume)
Urine Specific Gravity < 1.010 prior to start of chemotherapy
Urine output: Before infusion: > 100 mL/m^2/hour (or 3 mL/kg/hour)
After infusion: > 65 mL/m^2/hour (or 2 mL/kg/hour)
Monitoring for hematuria: at least every 8 hours
Monitor serum electrolytes
Dilution: Dilute ifosfamide in 80-125 mL/m^2 (at least 20 mg/mL) compatible IV fluid (D5W or NS only) (standardize volumes to nearest available sizes eg. 50, 100, 250mL)
Infusion time for doses ≤ 1800 mg/m^2/day should be 1hour.

5.3.2 Etoposide
Etoposide 100 mg/m^2/day IV infusion over 1 to 2 hours, Days 1-5 of each cycle. (500 mg/m^2 total dose)

For children < 1 year treat with 50% doses calculated on a m^2 basis. If tolerated (no delay in administration of the next cycle due to delayed count recovery or delayed resolution of other toxicities and no serious toxicities), consider increasing to 75% and then to 100% of the calculated full dose.

Recommendations:
Dilution: Administer etoposide at a concentration of ≤ 0.4 mg/mL in D5W or NS (utilize standard dilution volumes eg. 50, 100, 250, 500 mL); avoid use of large volumes of D5W due to potential development of hyponatremia
Rate of infusion: 100 mg/m^2/hour or 3.3 mg/kg/hr (**minimum** infusion time 1 hour)
Filtration: Utilize in-line filter during infusion due to potential precipitation formation
Peristaltic pumps: administration of etoposide via peristaltic pumps (e.g. CADD®, Pancretec®) is discouraged due to associated precipitation of etoposide
Monitoring: blood pressure, allergic reactions, inspect solution and tubing for precipitation before and during infusion.

5.3.3 MESNA
The use of MESNA with cyclophosphamide and ifosfamide is required. In the past, MESNA was held during radiation therapy. There are no data to suggest MESNA is a radioprotector. MESNA will therefore not be held during radiation therapy. The total daily MESNA dose is equal to at least 60% of the daily cyclophosphamide or ifosfamide dose (for example, 20% of the cyclophosphamide or ifosfamide dose in the bag with the drug and 2 boluses of the same dose at hours 4 and 8 after the infusion), or by continuous infusion of the 60% dose. MESNA continuous infusion should be started at the same time as the cyclophosphamide/ifosfamide and be completed no sooner than 8 hours after the end of the cyclophosphamide or ifosfamide infusion (e.g. with a one hour cyclophosphamide infusion, the MESNA continuous infusion would be at least 9 hours). The oral dose of MESNA is 2x the IV dose. Patients able to tolerate

oral MESNA may receive the final dose by mouth at 40% of the oxazaphosphorine (cyclophosphamide or ifosfamide) dose.

5.3.4 G-CSF (Filgrastim)
G-CSF (Filgrastim) 5 micrograms/kg/day **subcutaneously** beginning 24 hours after the last dose of chemotherapy (which may mean giving the dose in the evening), and continuing until the absolute neutrophil count is 750/μL or greater.

Note regarding GM-CSF (Sargramostim): In an NCI pilot study, GM-CSF did not permit interval compression of chemotherapy (24). **Do not substitute GM-CSF for G-CSF (Filgrastim) in this study.**

5.4 Timing of Chemotherapy

5.4.1 Obtaining Blood Counts
CBC with differential and platelet count should be obtained on Day 7 and 14 of each chemotherapy cycle. Patients on Regimen B (compressed chemotherapy) should obtain blood counts every Monday, Wednesday, and Friday after Day 14, until the criteria for beginning the next course are satisfied. Blood counts may be performed at the treating institution, or at any reliable outside laboratory, as long as the results are communicated the same day to the treating institution.

5.4.1.1
Blood count criteria and management: Chemotherapy cycles should begin at the specified intervals, or when the following blood count criteria are satisfied, whichever occurs later:

Absolute neutrophil count ≥ 750/μL
Platelet count ≥ 75,000/μL (without transfusion)

When the ANC is ≥ 750/μL and the platelet count is at least ≥ 75,000/μL stop the G-CSF and admit for chemotherapy. G-CSF (Filgrastim) must be stopped 24 hours before chemotherapy administration.

5.4.1.2
Counts may be rechecked on admission, but **chemotherapy should proceed even if the ANC has fallen after discontinuing G-CSF (Filgrastim).** This was the practice in the pilot study (671 evaluable cycles of chemotherapy in 71 patients), and worked well (14).

5.4.1.3
If another toxicity (e.g. mucositis) continues after the counts are satisfactory, the patient's status should be monitored daily, and the next cycle of chemotherapy begun within 48 hours of the resolution of the toxicity.

5.4.2 Regimen A Timing
Chemotherapy cycles should begin every 21 days except where surgery is indicated/scheduled as outlined in Section 5.1 (i.e., Day 22 of the previous cycle is Day 1 of the next cycle). Patients should have complete blood counts checked at Day 7 and Day 14 of each cycle.