

Regimen Reference Order

LEUK – CALGB 10403 (Delayed Intensification)

ARIA: LEUK - [CALGB 10403 (Del Intens)]

ARIA Support: LEUK - [CALGB 10403(Del Int) IT]

Planned Course: Single cycle (1 Cycle = 50 days)

Indication for Use: Newly Diagnosed Precursor B-Cell Acute Lymphoblastic Leukemia

CVAD: Preferred (VESICANT INVOLVED)

Proceed with treatment if:

Days 1 and 29

ANC equal to or greater than $0.75 \times 10^9/L$ AND Platelets equal to or greater than $75 \times 10^9/L$

❖ **Contact Leukemia/BMT (L/BMT) Physician if parameters not met**

SEQUENCE OF MEDICATION ADMINISTRATION

Pre-treatment Requirements

Drug	Dose	CCMB Administration Guideline
Not Applicable		

Treatment Regimen – LEUK – CALGB 10403 (Delayed Intensification)

Establish primary solution 500 mL of: normal saline

Drug	Dose	CCMB Administration Guideline
Day 1		
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
vinCRISTine	1.5 mg/m ² ; maximum dose 2 mg	IV in normal saline 25 mL over 2 to 3 minutes by gravity infusion
DOXOrubicin	25 mg/m ²	IV push over 10 minutes
dexamethasone	5 mg/m ² (round to nearest 2 mg) (see <i>Appendix B</i> for dexamethasone dosing instructions)	Orally twice daily with food (Self-administered at home)
Days 2 and 3		
dexamethasone	5 mg/m ² (round to nearest 2 mg) (see <i>Appendix B</i> for dexamethasone dosing instructions)	Orally twice daily with food (Self-administered at home)

Day 4		
dexamethasone	5 mg/m ² (round to nearest 2 mg) (see <i>Appendix B</i> for dexamethasone dosing instructions)	Orally twice daily with food (Self-administered at home)
acetaminophen	650 mg	Orally 1 hour prior to pegaspargase
hydrocortisone	100 mg	IV in normal saline 50 mL over 15 minutes 1 hour prior to pegaspargase <i>*Nursing Alert: pegaspargase starts 1 hour after completion of hydrocortisone</i>
famotidine	20 mg	IV in normal saline 50 mL over 15 minutes
diphenhydramine	50 mg	IV in normal saline 50 mL over 15 minutes
Wait 30 minutes after completion of IV pre-medication(s) before starting pegaspargase		
pegaspargase	1000 units/m ² ; maximum dose 1875 units	IV in normal saline 100 mL over 1 hour
Days 5 to 7		
dexamethasone	5 mg/m ² (round to nearest 2 mg) (see <i>Appendix B</i> for dexamethasone dosing instructions)	Orally twice daily with food (Self-administered at home)
Day 8		
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
vinCRISTine	1.5 mg/m ² ; maximum dose 2 mg	IV in normal saline 25 mL over 2 to 3 minutes by gravity infusion
DOXOrubicin	25 mg/m ²	IV push over 10 minutes
Day 15		
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
vinCRISTine	1.5 mg/m ² ; maximum dose 2 mg	IV in normal saline 25 mL over 2 to 3 minutes by gravity infusion
DOXOrubicin	25 mg/m ²	IV push over 10 minutes
dexamethasone	5 mg/m ² (round to nearest 2 mg) (see <i>Appendix B</i> for dexamethasone dosing instructions)	Orally twice daily with food (Self-administered at home)

Days 16 to 21		
dexamethasone	5 mg/m ² (round to nearest 2 mg) (see <i>Appendix B</i> for dexamethasone dosing instructions)	Orally twice daily with food (Self-administered at home)
Day 29		
normal saline	1000 mL	IV over 1 hour (Pre hydration)
aprepitant	125 mg	Orally 1 hour pre-chemotherapy
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
dexamethasone	12 mg	Orally 30 minutes pre-chemotherapy
cyclophosphamide	1000 mg/m ²	IV in normal saline 250 mL over 1 hour
cytarabine	75 mg/m ²	IV push over 2 to 5 minutes
thioguanine	60 mg/m ² (see <i>Appendix A</i> and <i>Appendix B</i> for thioguanine dosing instructions)	Orally once on an empty stomach Do not crush or chew (Self-administered at home)
Days 30 to 32		
cytarabine	75 mg/m ²	IV push over 2 to 5 minutes
thioguanine	60 mg/m ² (see <i>Appendix A</i> and <i>Appendix B</i> for thioguanine dosing instructions)	Orally once daily on an empty stomach Do not crush or chew (Self-administered at home)
Days 33 to 35		
thioguanine	60 mg/m ² (see <i>Appendix A</i> and <i>Appendix B</i> for thioguanine dosing instructions)	Orally once daily on an empty stomach Do not crush or chew (Self-administered at home)
Days 36 to 39		
cytarabine	75 mg/m ²	IV push over 2 to 5 minutes
thioguanine	60 mg/m ² (see <i>Appendix A</i> and <i>Appendix B</i> for thioguanine dosing instructions)	Orally once daily on an empty stomach Do not crush or chew (Self-administered at home)

Days 40 to 42		
thioguanine	60 mg/m ² (see <i>Appendix A</i> and <i>Appendix B</i> for thioguanine dosing instructions)	Orally once daily on an empty stomach Do not crush or chew (Self-administered at home)
Day 43		
vinCRIS ^{ti} ne	1.5 mg/m ² ; maximum dose 2 mg	IV in normal saline 25 mL over 2 to 3 minutes by gravity infusion
acetaminophen	650 mg	Orally 1 hour prior to pegaspargase
hydrocortisone	100 mg	IV in normal saline 50 mL over 15 minutes 1 hour prior to pegaspargase <i>*Nursing Alert: pegaspargase starts 1 hour after completion of hydrocortisone</i>
famotidine	20 mg	IV in normal saline 50 mL over 15 minutes
diphenhydramINE	50 mg	IV in normal saline 50 mL over 15 minutes
Wait 30 minutes after completion of IV pre-medication(s) before starting pegaspargase		
pegaspargase	1000 units/m ² ; maximum dose 1875 units	IV in normal saline 100 mL over 1 hour
Day 50		
vinCRIS ^{ti} ne	1.5 mg/m ² ; maximum dose 2 mg	IV in normal saline 25 mL over 2 to 3 minutes by gravity infusion
Patients will receive methotrexate Intrathecal Therapy with this regimen (See <i>Appendix C</i> – Intrathecal Therapy (IT))		
See <i>Appendix D</i> – Delayed Intensification Dosing Schema		
thioguanine (LANVIS [®]) available dosage strength: 40 mg tablet Classification: Cytotoxic, Hazardous		

In the event of an infusion-related hypersensitivity reaction, refer to the 'Hypersensitivity Reaction Standing Order'

REQUIRED MONITORING

Cardiac Monitoring

- Left Ventricular Ejection Fraction (LVEF) monitoring is recommended at baseline and as clinically indicated

Day 1

- CBC, serum creatinine, urea, electrolytes, liver enzymes, total bilirubin and glucose as per Physician Orders
- Glucose and lipase as per Physician Orders

Day 4

- Fibrinogen as per Physician Orders
- Full vital signs (temperature, heart rate, respiratory rate, blood pressure and O₂ saturation) at baseline and as clinically indicated during pegaspargase administration
- Observe patient for 1 hour after administration of pegaspargase. Full vital signs before discharge

Days 15, 36 and 50

- Glucose and lipase as per Physician Orders

Day 29

- CBC, serum creatinine, urea, electrolytes, liver enzymes, total bilirubin and glucose as per Physician Orders

Day 43

- Fibrinogen, glucose and lipase as per Physician Orders
- Full vital signs (temperature, heart rate, respiratory rate, blood pressure and O₂ saturation) at baseline and as clinically indicated during pegaspargase administration
- Observe patient for 1 hour after administration of pegaspargase. Full vital signs before discharge

Recommended Support Medications

Drug	Dose	CCMB Administration Guideline
valACYclovir	500 mg	Orally twice daily
sulfamethoxazole-trimethoprim	800/160 mg	Orally once daily on Mondays, Wednesdays and Fridays
aprepitant	80 mg	Orally once daily on Days 30 and 31
metoclopramide	10 mg	Orally every 4 hours while awake on Days 9 and 10
metoclopramide	10 – 20 mg	Orally every 4 hours as needed for nausea and vomiting (excluding Days 9 and 10)

DISCHARGE INSTRUCTIONS

- Patients should be instructed to contact their cancer team immediately if symptoms of hypersensitivity reactions occur after discharge
 - Instruct patient to:
 - Continue taking anti-emetic(s) at home
 - Maintain oral intake of 2000 mL (8 glasses) of fluid daily at home
 - Empty bladder every 2 hours while awake and at bedtime for 24 hours after cyclophosphamide treatment
 - Obtain immediate assistance as per your clinic's contact instructions if:
 - Symptoms of hemorrhagic cystitis (e.g. dysuria, hematuria)
 - Unable to drink recommended amount of fluid
 - thioguanine and dexamethasone are cancer therapies in this treatment regimen. Remind patient to take thioguanine and dexamethasone at home. See *Appendix B* for dexamethasone and thioguanine prescriptions
 - thioguanine should not be taken with milk or citrus based products
 - Remind patient to take valACYclovir (shingles prophylaxis) and sulfamethoxazole-trimethoprim (*Pneumocystis jirovecii* pneumonia prophylaxis) at home
 - Instruct patient to hold sulfamethoxazole-trimethoprim on days when intrathecal methotrexate is administered
 - Reinforce safe handling precautions of medications, blood and body fluids for 48 hours after completion of chemotherapy
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ADDITIONAL INFORMATION

- Physician or designate must be on site in case of reactions to pegaspargase
 - Do not administer on weekends or holidays
- pegaspargase can cause anaphylaxis. diphenhydrAMINE, hydrocortisone and EPINEPHrine must be available in case of reaction
- pegaspargase can cause serious side effects such as hemorrhage, pancreatitis and thrombotic events
- sulfamethoxazole-trimethoprim should not be administered on days when intrathecal methotrexate is administered due to potential drug interaction
- Total daily dose of dexamethasone is calculated and then divided twice daily. Since dexamethasone is rounded to the nearest 2 mg tablet, this may result in a higher dose in the morning than in the afternoon. Due to limitations in ARIA, the prescription for dexamethasone is built as "Take as Directed". When prescribing, the Admin Instructions must be modified to include the appropriate dose
- thioguanine is dosed with a weekly target dose of 420 mg/m² (Days 29 to 42). Doses are given at least one hour after the evening meal. Different daily doses rounded to the nearest 20 mg are to be given on alternating days when required to attain the weekly target dose. See *Appendix A* for administration instructions for thioguanine prescriptions
- pegaspargase dose reduction is recommended for patients with fatty liver or BMI over 30 kg/m² (dose reduce to pegaspargase 500 units/m²)
- thioguanine may be eligible for Home Cancer Drug Program coverage
- Intrathecal therapy is part of this regimen to start on Day 1 of CALGB 10403 (Delayed Intensification). See *Appendix C* regarding dosing for the support regimen LEUK - [CALGB 10403(Del Int) IT]. Support protocol is available under **CALGB (Del Int IT)** in the "Leukemia" folder

Appendix A

thioguanine Dosing – LEUK – CALGB 10403 (Delayed Intensification)

thioguanine dose is calculated by the Leukemia/BMT clinic

In the LEUK – CALGB 10403 (Delayed Intensification) regimen, thioguanine should be dosed at 60 mg/m²/day on Days 29 to 42 of the 50-day cycle (Weekly dose of 420 mg/m²). Because thioguanine is only available as a 40 mg tablet, there is limited flexibility in delivering the appropriate daily dose. As such, the dosing schedule may require different daily doses to ensure an appropriate dose over the course of the cycle.

While the Medical Oncology Manager (ARIA®) application is used for order entry and a specific regimen for the LEUK – CALGB 10403 (Delayed Intensification) regimen is available, the dosing instructions for this regimen are too complex to build into the ARIA-based regimen. Manual calculation and manual entry of the dosing instructions (e.g. number of tablets per dose) is required. The table below outlines required tablets per dose according to patient body surface area.

Administration Instructions on Day 29:

Take dose orally once daily for 14 days starting Day 29

Take on an empty stomach at least one hour after the evening meal

Avoid milk and citrus based products at the same time as the dose

Target dose = 60 mg/m² PO on Days 29 to 42 (Weekly dose 420 mg/m²/week)

Medication may be eligible for Home Cancer Drug Program coverage

thioguanine Dosing Instructions

thioguanine dosing for daily doses of 60 mg/m² (Target weekly dose of 420 mg/m²) administered on Days 29 to 42

BSA (m²)	7-day daily dose* 1 tab = 40 mg	Dosing Instructions for Days 29 to 42**
1.2-1.24	2 tablets/day x 4; 1½ tablets/day x 3 (500 mg/week)	Take 60 mg (1 & 1/2 tablets) once daily on Mondays, Wednesdays and Fridays and 80 mg (2 tablets) once daily on Tuesdays, Thursdays, Saturdays and Sundays Qty: 25 of 40 mg tablets
1.25-1.29	2 tablets/day x 5; 1½ tablets/day x 2 (520 mg/week)	Take 60 mg (1 & 1/2 tablets) once daily on Thursdays and Sundays and 80 mg (2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays and Saturdays Qty: 26 x 40 mg tablets
1.3-1.34	2 tablets/day x 6; 1½ tablets/day x 1 (540 mg/week)	Take 60 mg (1 & 1/2 tablets) once daily on Thursdays and 80 mg (2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays, Saturdays and Sundays Qty: 27 x 40 mg tablets
1.35-1.39	2 tablets/day x 7 (560 mg/week)	Take 80 mg (2 tablets) orally once daily Qty: 28 x 40 mg tablets
1.4-1.44	2 tablets/day x 6; 2½ tablets/day x 1 (580 mg/week)	Take 100 mg (2 & 1/2 tablets) once daily on Thursdays and 80 mg (2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays, Saturdays and Sundays Qty: 29 x 40 mg tablets
1.45-1.49	2 tablets/day x 5; 2½ tablets/day x 2 (600 mg/week)	Take 100 mg (2 & 1/2 tablets) once daily on Thursdays and Sundays and 80 mg (2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays and Saturdays Qty: 30 x 40 mg tablets
1.5-1.54	2 tablets/day x 4; 2½ tablets/day x 3 (620 mg/week)	Take 100 mg (2 & 1/2 tablets) once daily on Mondays, Wednesdays and Fridays and 80 mg (2 tablets) once daily on Tuesdays, Thursdays, Saturdays and Sundays Qty: 31 x 40 mg tablets
1.55-1.59	2½ tablets day x 4; 2 tablets/day x 3 (640 mg/week)	Take 80 mg (2 tablets) once daily on Mondays, Wednesdays and Fridays and 100 mg (2 & 1/2 tablets) once daily on Tuesdays, Thursdays, Saturdays and Sundays Qty: 32 x 40 mg tablets
1.6-1.64	2½ tablets/day x 5; 2 tablets/day x 2 (660 mg/week)	Take 80 mg (2 tablets) once daily on Thursdays and Sundays and 100 mg (2 & 1/2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays and Saturdays Qty: 33 x 40 mg tablets

1.65-1.69	2½ tablets/day x 6; 2 tablets/day x 1 (680 mg/week)	Take 80 mg (2 tablets) once daily on Thursdays and 100 mg (2 & 1/2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays, Saturdays and Sundays Qty: 34 x 40 mg tablets
1.7-1.74	2½ tablets/day x 7 (700 mg/week)	Take 100 mg (2 & 1/2 tablets) orally once daily Qty: 35 x 40 mg tablets
1.75-1.79	2½ tablets/day x 6; 3 tablets/day x 1 (720 mg/week)	Take 120 mg (3 tablets) once daily on Thursdays and 100 mg (2 & 1/2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays, Saturdays and Sundays Qty: 36 x 40 mg tablets
1.8-1.84	2½ tablets/day x 5; 3 tablets/day x 2 (740 mg/week)	Take 120 mg (3 tablets) once daily on Thursdays and Sundays and 100 mg (2 & 1/2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays and Saturdays Qty: 37 x 40 mg tablets
1.85-1.89	2½ tablets/day x 4; 3 tablets/day x 3 (760 mg/week)	Take 120 mg (3 tablets) once daily on Mondays, Wednesdays and Fridays and 100 mg (2 & 1/2 tablets) once daily on Tuesdays, Thursdays, Saturdays and Sundays Qty: 38 x 40 mg tablets
1.9-1.94	3 tablets/day x 4; 2½ tablets/day x 3 (780 mg/week)	Take 100 mg (2 & 1/2 tablets) once daily on Mondays, Wednesdays and Fridays and 120 mg (3 tablets) once daily on Tuesdays, Thursdays, Saturdays and Sundays Qty: 39 x 40 mg tablets
1.95-1.99	3 tablets/day x 5; 2½ tablets/day x 2 (800 mg/week)	Take 100 mg (2 & 1/2 tablets) once daily on Thursdays and Sundays and 120 mg (3 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays and Saturdays Qty: 40 x 40 mg tablets
2-2.04	3 tablets/day x 6; 2½ tablets/day x 1 (820 mg/week)	Take 100 mg (2 & 1/2 tablets) once daily on Thursdays and 120 mg (3 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays, Saturdays and Sundays Qty: 41 x 40 mg tablets
<p>* The 7-day daily dose refers to the weekly dose to attain the weekly target dose of 420 mg/m²</p> <p>** Dosing Instructions for Day 29 can be used for the administration instruction field of the ARIA prescription for the relevant BSA. Required days of the week and dispensing quantities are included in the instructions.</p> <p>Due to limitations in ARIA the prescription for thioguanine has a default dose of 1 mg/m². When prescribing it is advised to modify the prescription from “Complex” to “Take as Directed” and to populate the Admin Instructions with the relevant instructions from this table (Dosing Instructions for Days 29 to 42) and Administration Instructions from Page 7.</p> <p>Patients with thiopurine methyltransferase (TPMT) deficiency require dose reductions during therapy. Please refer to original protocol for details. (When myelosuppression has led to significant delays in therapy (greater than 2 weeks) or is disproportionate to the therapy, thiopurine methyltransferase testing should be performed)</p>		

Appendix B

dexamethasone and thioguanine prescriptions		
Drug	Dose	CCMB Administration Guideline
dexamethasone	5 mg/m ² (to nearest 2 mg)	Orally twice daily with food on Days 1 to 7 and Days 15 to 21
thioguanine	60 mg/m ² (see <i>Appendix A</i> for thioguanine dosing instructions)	Orally once daily on an empty stomach on Days 29 to 42 Do not crush or chew

Appendix C**Intrathecal Therapy (IT) – LEUK - [CALGB 10403(Del Int) IT]**

Proceed with treatment if:

- *Platelets equal to or greater than $50 \times 10^9/L$*

Days 1, 29 and 36

Drug	Dose	CCMB Administration Guideline
methotrexate	15 mg	Intrathecal in 6 mL preservative free normal saline administered in L/BMT Clinic

IT is ordered as a separate support regimen to start on Day 1 of CALGB 10403 (Delayed Intensification)

Appendix D
Delayed Intensification Dosing Schema

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	
vinCRiStine 1.5 mg/m ² IV; maximum dose 2 mg																										
DOXOrubicin 25 mg/m ² IV																										
dexamethasone 5 mg/m ² orally twice daily																										
pegaspargase 1000 units/m ² IV; maximum dose 1875 units																										

Day	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	
vinCRiStine 1.5 mg/m ² IV; maximum dose 2 mg																										
pegaspargase 1000 units/m ² IV; maximum dose 1875 units																										
cyclophosphamide 1000 mg/m ² IV																										
cytarabine 75 mg/m ² IV																										
thioguanine 60 mg/m ² orally once daily																										

Key: ■ indicates that this medication will be administered on this day