

Regimen Reference Order – LEUK – CALGB 10403 (Maintenance)

ARIA: LEUK - [CALGB 10403 (Maint)]

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

Planned Course: 1 Cycle = 12 weeks (84 days)
 Repeat Maintenance Therapy (12-week (84 day) cycles) until total duration of therapy is 2 years from start of Interim Maintenance Therapy for female patients, or 3 years from start of Interim Maintenance Therapy for male patients

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

CVAD: Preferred (VESICANT INVOLVED)

<p><u>Proceed with treatment if:</u></p> <p>Day 1</p> <ul style="list-style-type: none"> ANC equal to or greater than $0.75 \times 10^9/L$ AND Platelets equal to or greater than $75 \times 10^9/L$ <p>Days 29 and 57</p> <ul style="list-style-type: none"> ANC equal to or greater than $0.5 \times 10^9/L$ AND Platelets equal to or greater than $75 \times 10^9/L$ <p>Note: Only mercaptopurine and methotrexate will be interrupted for myelosuppression</p> <ul style="list-style-type: none"> ❖ Contact Leukemia/BMT (L/BMT) Physician if parameters not met
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SEQUENCE OF MEDICATION ADMINISTRATION

Pre-treatment Requirements		
Drug	Dose	CCMB Administration Guideline
Not Applicable		

Treatment Regimen – LEUK – CALGB 10403 (Maintenance)		
Establish primary solution 500 mL of: normal saline		
Drug	Dose	CCMB Administration Guideline
Days 1 to 84		
mercaptopurine	75 mg/m ² * (see Appendix A and Appendix B for mercaptopurine dosing instructions)	Orally once daily on an empty stomach Do not crush or chew (Self-administered at home)
Day 1		
vinCRISatine	1.5 mg/m ² ; maximum dose 2 mg	IV in normal saline 25 mL over 2 to 3 minutes by gravity infusion

dexamethasone	6 mg/m ² /day (round to nearest 2 mg) (see <i>Appendix B</i> for dexamethasone dosing instructions)	Orally divided twice daily with food (Self-administered at home)
Days 2 to 5		
dexamethasone	6 mg/m ² /day (round to nearest 2 mg) (see <i>Appendix B</i> for dexamethasone dosing instructions)	Orally divided twice daily with food (Self-administered at home)
Days 8, 15 and 22		
methotrexate	20 mg/m ² * (round to nearest 2.5 mg) (see <i>Appendix B</i> for methotrexate dosing instructions)	Orally once weekly on an empty stomach in the evening (Self-administered at home) <i>*Nursing Alert: patient will be instructed to hold sulfamethoxazole-trimethoprim on days when methotrexate is administered</i>
Day 29		
vinCRIStine	1.5 mg/m ² ; maximum dose 2 mg	IV in normal saline 25 mL over 2 to 3 minutes by gravity infusion
dexamethasone	6 mg/m ² /day (round to nearest 2 mg) (see <i>Appendix B</i> for dexamethasone dosing instructions)	Orally divided twice daily with food (Self-administered at home)
methotrexate	Cycles 1 to 4: No methotrexate given on Day 29	Cycles 1 to 4: <i>*Alert: oral methotrexate is held on Day 29 for the first 4 cycles of maintenance therapy as IT methotrexate is given instead</i>
	Cycle 5 and Onwards: 20 mg/m ² * (round to nearest 2.5 mg) (see <i>Appendix B</i> for methotrexate dosing instructions)	Cycle 5 and Onwards only: Orally once on an empty stomach in the evening (Self-administered at home) <i>*Nursing Alert: patient will be instructed to hold sulfamethoxazole-trimethoprim on days when methotrexate is administered</i>
Days 30 to 33		
dexamethasone	6 mg/m ² /day (round to nearest 2 mg) (see <i>Appendix B</i> for dexamethasone dosing instructions)	Orally divided twice daily with food (Self-administered at home)

Days 36, 43 and 50		
methotrexate	20 mg/m ² * (round to nearest 2.5 mg) (see <i>Appendix B</i> for methotrexate dosing instructions)	Orally once weekly on an empty stomach in the evening (Self-administered at home) <i>*Nursing Alert: patient will be instructed to hold sulfamethoxazole-trimethoprim on days when methotrexate is administered</i>
Day 57		
vinCRIStine	1.5 mg/m ² ; maximum dose 2 mg	IV in normal saline 25 mL over 2 to 3 minutes by gravity infusion
dexamethasone	6 mg/m ² /day (round to nearest 2 mg) (see <i>Appendix B</i> for dexamethasone dosing instructions)	Orally divided twice daily with food (Self-administered at home)
methotrexate	20 mg/m ² * (round to nearest 2.5 mg) (see <i>Appendix B</i> for methotrexate dosing instructions)	Orally once on an empty stomach in the evening (Self-administered at home) <i>*Nursing Alert: patient will be instructed to hold sulfamethoxazole-trimethoprim on days when methotrexate is administered</i>
Days 58 to 61		
dexamethasone	6 mg/m ² /day (round to nearest 2 mg) (see <i>Appendix B</i> for dexamethasone dosing instructions)	Orally divided twice daily with food (Self-administered at home)
Days 64, 71 and 78		
methotrexate	20 mg/m ² * (round to nearest 2.5 mg) (see <i>Appendix B</i> for methotrexate dosing instructions)	Orally once weekly on an empty stomach in the evening (Self-administered at home) <i>*Nursing Alert: patient will be instructed to hold sulfamethoxazole-trimethoprim on days when methotrexate is administered</i>
<p><i>*The dose of mercaptopurine (or methotrexate) is escalated by 25% from the previous dose if ANC equal to or greater than 1.5 x 10⁹/L on 3 CBC(s) done over 6 weeks or 2 successive monthly CBCs. If same parameters are met, the alternating drug (methotrexate (or mercaptopurine)) is next escalated by 25%.</i></p> <p><i>mercaptopurine and methotrexate doses may also be decreased for toxicity (bilirubin, AST or ALT elevations) according to protocol. Dose adjustments are made as per the Leukemia/BMT (L/BMT) Physician's discretion according to protocol</i></p> <p>mercaptopurine and methotrexate doses are calculated by the Leukemia/BMT clinic</p>		
<p>Patients will receive methotrexate Intrathecal Therapy with this regimen (See <i>Appendix C – Intrathecal Therapy (IT)</i>)</p>		

See Appendix D – Maintenance Dosing Schema

mercaptopurine (PURINETHOL®) available dosage strength: 50 mg tablet

Classification: Cytotoxic, Hazardous

methotrexate available dosage strengths: 2.5 mg and 10 mg tablets

Classification: Cytotoxic, Hazardous

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

REQUIRED MONITORING

Days 1, 29 and 57

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

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

DISCHARGE INSTRUCTIONS

- mercaptopurine, dexamethasone and methotrexate are cancer therapies in this treatment regimen. Remind patient to take mercaptopurine, dexamethasone and methotrexate at home. See *Appendix B* for mercaptopurine, dexamethasone and methotrexate prescriptions
- mercaptopurine should not be taken with milk or citrus based products. Cow’s milk in particular, contains high concentrations of xanthine oxidase which inactivates mercaptopurine
- 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 or oral methotrexate is administered
- Reinforce safe handling precautions of medications, blood and body fluids for 48 hours after completion of chemotherapy

ADDITIONAL INFORMATION

- sulfamethoxazole-trimethoprim should not be administered on days when intrathecal or oral methotrexate is administered due to potential drug interaction
- valACYclovir (shingles prophylaxis) and sulfamethoxazole-trimethoprim (*Pneumocystis jirovecii* pneumonia prophylaxis) continue while on treatment and for 6 months after discontinuation of treatment
- All CNS3 patients who achieve a complete remission (CR) will receive cranial radiation therapy during the first cycle of Maintenance Therapy
- Total daily dose of dexamethasone is calculated and then divided twice daily. Since dexamethasone is rounded to the nearest 2 mg, 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
- mercaptopurine is dosed with a weekly target dose of 525 mg/m² (Days 1 to 84). Doses are given at least one hour after the evening meal. Different daily doses rounded to the nearest 25 mg are to be given on alternating days when required to attain the weekly target dose. See *Appendix A* for administration instructions for mercaptopurine prescriptions
- mercaptopurine and methotrexate may be eligible for Home Cancer Drug Program coverage
- Intrathecal therapy is part of this regimen to start on Day 1 of CALGB 10403 (Maintenance). See *Appendix C* regarding dosing for the support regimen LEUK - [CALGB 10403(Maint) IT]. Support protocol is available under **CALGB (Maint IT)** in the “Leukemia” folder

Appendix A

mercaptopurine Dosing – LEUK – CALGB 10403 (Maintenance)

mercaptopurine dose is calculated by the Leukemia/BMT clinic

In the LEUK – CALGB 10403 (Maintenance) regimen, mercaptopurine should be dosed at 75 mg/m²/day on Days 1 to 84 of the 84-day cycle (Weekly dose of 525 mg/m²). Because mercaptopurine is only available as a 50 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 (Maintenance) 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 1:

Take dose orally once daily for 28 days starting Day 1
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 = 75 mg/m² PO on Days 1 to 28 (Weekly dose 525 mg/m²/week)

Medication may be eligible for Home Cancer Drug Program coverage

Administration Instructions on Day 29:

Take dose orally once daily for 28 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 = 75 mg/m² PO on Days 29 to 56 (Weekly dose 525 mg/m²/week)

Medication may be eligible for Home Cancer Drug Program coverage

Administration Instructions on Day 57:

Take dose orally once daily for 28 days starting Day 57
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 = 75 mg/m² PO on Days 57 to 84 (Weekly dose 525 mg/m²/week)

Medication may be eligible for Home Cancer Drug Program coverage

mercaptopurine Dosing Instructions

mercaptopurine dosing for daily doses of 75 mg/m² (Target weekly dose of 525 mg/m²) administered on Days 1 to 84

**Note: mercaptopurine may be dose escalated based on CBC results or may be dose reduced for toxicity*

BSA (m²)	7-day daily dose* 1 tab = 50 mg	Dosing Instructions for Days 1 to 28 and Days 29 to 56 and Day 57 to 84**
1.25 – 1.29	2 tablets/day x 5; 1½ tablets/day x 2 (650 mg/week)	Take 75 mg (1 & 1/2 tablets) once daily on Thursdays and Sundays and 100 mg (2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays and Saturdays Qty: 52 x 50 mg tablets
1.3 – 1.34	2 tablets/day x 6; 1½ tablets/day x 1 (675 mg/week)	Take 75 mg (1 & 1/2 tablets) once daily on Thursdays and 100 mg (2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays, Saturdays and Sundays Qty: 54 x 50 mg tablets
1.35 – 1.39	2 tablets/day x 7 (700 mg/week)	Take 100 mg (2 tablets) orally once daily Qty: 56 x 50 mg tablets
1.4 – 1.44	2 tablets/day x 6; 2½ tablets/day x 1 (725 mg/week)	Take 125 mg (2 & 1/2 tablets) once daily on Thursdays and 100 mg (2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays, Saturdays and Sundays Qty: 58 x 50 mg tablets
1.45 – 1.49	2 tablets/day x 5; 2½ tablets/day x 2 (750 mg/week)	Take 125 mg (2 & 1/2 tablets) once daily on Thursdays and Sundays and 100 mg (2 tablets) on Mondays, Tuesdays, Wednesdays, Fridays and Saturdays Qty: 60 x 50 mg tablets
1.5 – 1.54	2 tablets/day x 4; 2½ tablets/day x 3 (775 mg/ week)	Take 125 mg (2 & 1/2 tablets) once daily on Mondays, Wednesdays and Fridays and 100 mg (2 tablets) once daily on Tuesdays, Thursdays, Saturdays and Sundays Qty: 62 x 50 mg tablets
1.55 – 1.59	2½ tablets/day x 4; 2 tablets/day x 3 (800 mg/week)	Take 100 mg (2 tablets) once daily on Mondays, Wednesdays and Fridays and 125 mg (2 & 1/2 tablets) once daily on Tuesdays, Thursdays, Saturdays and Sundays Qty: 64 x 50 mg tablets

1.6 – 1.64	2½ tablets/day x 5; 2 tablets/day x 2 (825 mg/week)	Take 100 mg (2 tablets) once daily on Thursdays and Sundays and 125 mg (2 & 1/2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays and Saturdays Qty: 66 x 50 mg tablets
1.65 – 1.69	2½ tablets/day x 6; 2 tablets/day x 1 (850 mg/week)	Take 100 mg (2 tablets) once daily on Thursdays and 125 mg (2 & 1/2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays, Saturdays and Sundays Qty: 68 x 50 mg tablets
1.7 – 1.74	2½ tablets/day x 7 (875 mg/week)	Take 125 mg (2 & 1/2 tablets) orally once daily Qty: 70 x 50 mg tablets
1.75 – 1.79	2½ tablets/day x 6; 3 tablets/day x 1 (900 mg/week)	Take 150 mg (3 tablets) once daily on Thursdays and 125 mg (2 & 1/2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays, Saturdays and Sundays Qty: 72 x 50 mg tablets
1.8 – 1.84	2½ tablets/day x 5; 3 tablets/day x 2 (925 mg/week)	Take 150 mg (3 tablets) once daily on Thursdays and Sundays and 125 mg (2 & 1/2 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays and Saturdays Qty: 74 x 50 mg tablets
1.85 – 1.89	2½ tablets/day x 4; 3 tablets/day x 3 (950 mg/week)	Take 150 mg (3 tablets) once daily on Mondays, Wednesdays and Fridays and 125 mg (2 & 1/2 tablets) once daily on Tuesdays, Thursdays, Saturdays and Sundays Qty: 76 x 50 mg tablets
1.9 – 1.94	3 tablets/day x 4; 2½ tablets/day x 3 (975 mg/week)	Take 125 mg (2 & 1/2 tablets) once daily on Mondays, Wednesdays and Fridays and 150 mg (3 tablets) once daily on Tuesdays, Thursdays, Saturdays and Sundays Qty: 78 x 50 mg tablets
1.95 – 1.99	3 tablets/day x 5; 2½ tablets/day x 2 (1000 mg/week)	Take 125 mg (2 & 1/2 tablets) once daily on Thursdays and Sundays and 150 mg (3 tablets) once daily on Mondays, Tuesdays, Wednesdays, Fridays and Saturdays Qty: 80 x 50 mg tablets
<p>* The 7-day daily dose refers to the weekly dose to attain the weekly target dose of 525 mg/m²</p> <p>** Dosing Instructions for Day 1, Day 29 and Day 57 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 mercaptopurine 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 1 to 28, Days 29 to 56 and Days 57 to 84) and Administration Instructions from Page 6.</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

mercaptopurine, dexamethasone and methotrexate prescriptions		
Drug	Dose	CCMB Administration Guideline
mercaptopurine	75 mg/m ² (see <i>Appendix A</i> for mercaptopurine dosing instructions)	Orally once daily on an empty stomach on Days 1 to 84 Do not crush or chew
dexamethasone	6 mg/m ² /day (to nearest 2 mg)	Orally divided twice daily with food on Days 1 to 5, Days 29 to 33 and Days 57 to 61
methotrexate	20 mg/m ² (to nearest 2.5 mg)	Cycles 1 to 4: Orally once weekly on an empty stomach in the evening on Days 8, 15, 22, 36, 43, 50, 57, 64, 71 and 78 <i>*Alert: oral methotrexate is held on Day 29 for the first 4 cycles of maintenance therapy as IT methotrexate is given instead</i>
		Cycle 5 and Onwards: Orally once weekly on an empty stomach in the evening on Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78

Appendix C

Intrathecal Therapy (IT) – LEUK - [CALGB 10403(Maint) IT]		
Proceed with treatment if: <ul style="list-style-type: none"> • <i>Platelets equal to or greater than 50 x 10⁹/L</i> 		
Cycles 1 to 4		
Days 1 and 29		
<i>** Note: patient is not to take oral methotrexate on Day 29 of Cycles 1 to 4</i>		
Drug	Dose	CCMB Administration Guideline
methotrexate	15 mg	Intrathecal in 6 mL preservative free normal saline administered in L/BMT Clinic
Cycle 5 and Onwards		
Day 1 only		
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 (Maintenance)		

Appendix D Maintenance 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	26	27	28
mercaptopurine 75 mg/m ² orally once daily	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
vinCRISStine 1.5 mg/m ² IV; maximum dose 2 mg	■																											
dexamethasone 6 mg/m ² /day orally divided twice daily	■	■	■	■	■																							
methotrexate 20 mg/m ² orally once weekly								■							■								■					

Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56
mercaptopurine 75 mg/m ² orally once daily	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
vinCRISStine 1.5 mg/m ² IV; maximum dose 2 mg	■																											
dexamethasone 6 mg/m ² /day orally divided twice daily	■	■	■	■	■																							
methotrexate 20 mg/m ² orally once weekly	*■							■							■								■					

Day	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84
mercaptopurine 75 mg/m ² orally once daily	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
vinCRISStine 1.5 mg/m ² IV; maximum dose 2 mg	■																											
dexamethasone 6 mg/m ² /day orally divided twice daily	■	■	■	■	■																							
methotrexate 20 mg/m ² orally once weekly	■							■							■								■					

Key: ■ indicates that this medication will be administered on this day
 *■ indicates that this medication will be administered on this day for Cycle 5 and onwards ONLY