

AALL15P1

A Group-Wide Pilot Study to Test the Tolerability and Biologic Activity of the Addition of Azacitidine (IND#133688, NSC# 102816) to Chemotherapy in Infants with Acute Lymphoblastic Leukemia (ALL) and KMT2A (MLL) Gene Rearrangement.

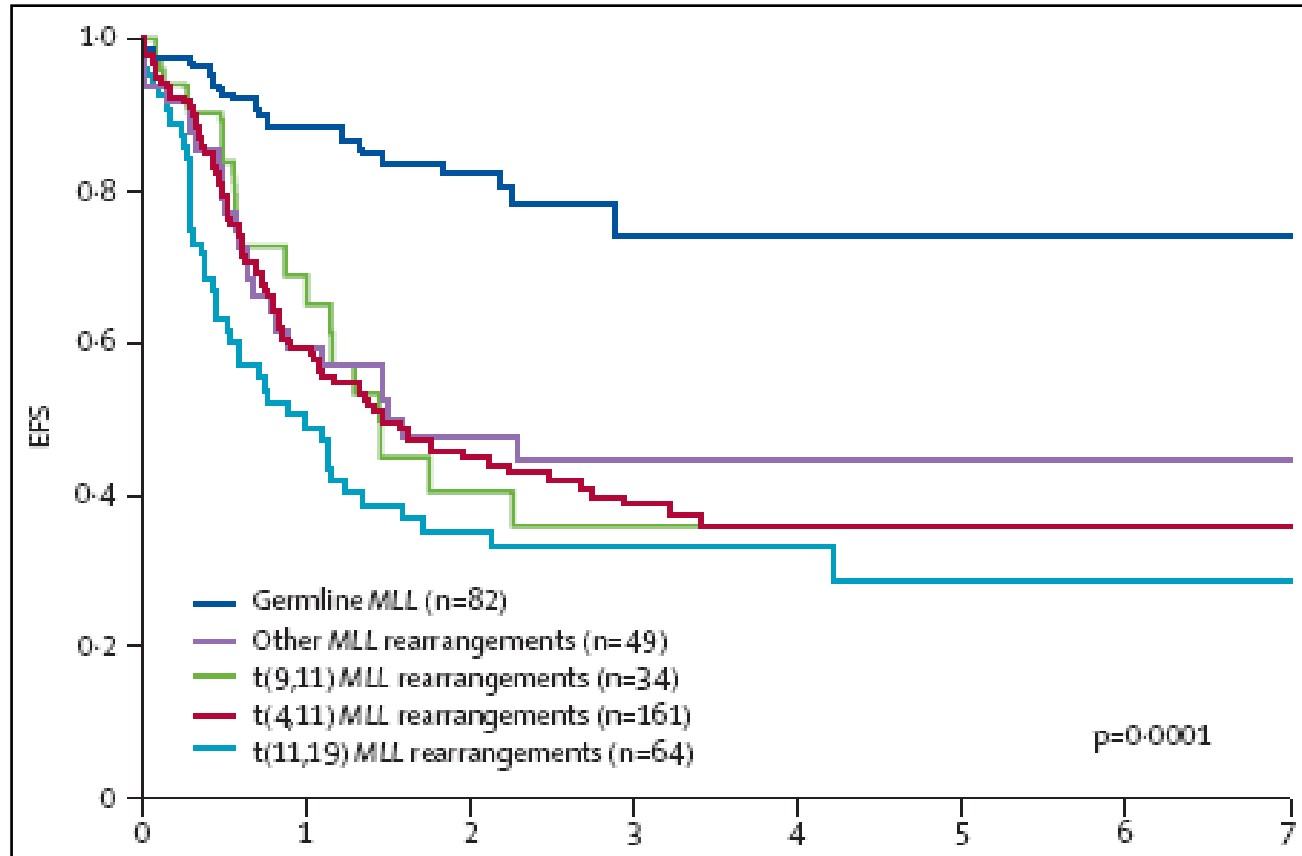
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Background

Approximately 75-80% of infant ALL cases contain the KMT2A mutations (previously Mixed Lineage Leukemia or MLL) and the survival rate for these patients remains poor.

MLL Rearrangement EFS



MLL or KMT2A rearrangements are involved in the development of acute leukemia, particularly in infants.

The chart on the right shows that there are different KMT2A rearrangements with varied prognosis inferior to the Germline MLL (see the  line).

AALL 15P1: Primary Aim

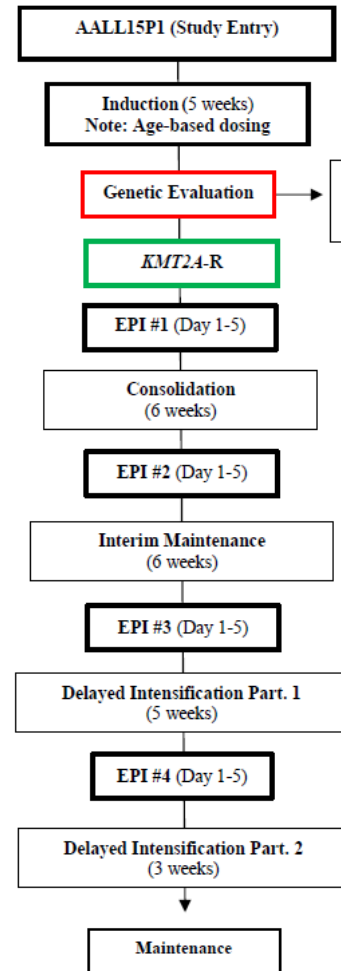
To evaluate the tolerability of azacitidine in addition to Interfant-06 standard chemotherapy in infants with newly diagnosed ALL with *KMT2A* gene rearrangement (*KMT2A*-R).

Azacitidine

It is a demethylating agent as well as an antimetabolite chemotherapy agent.

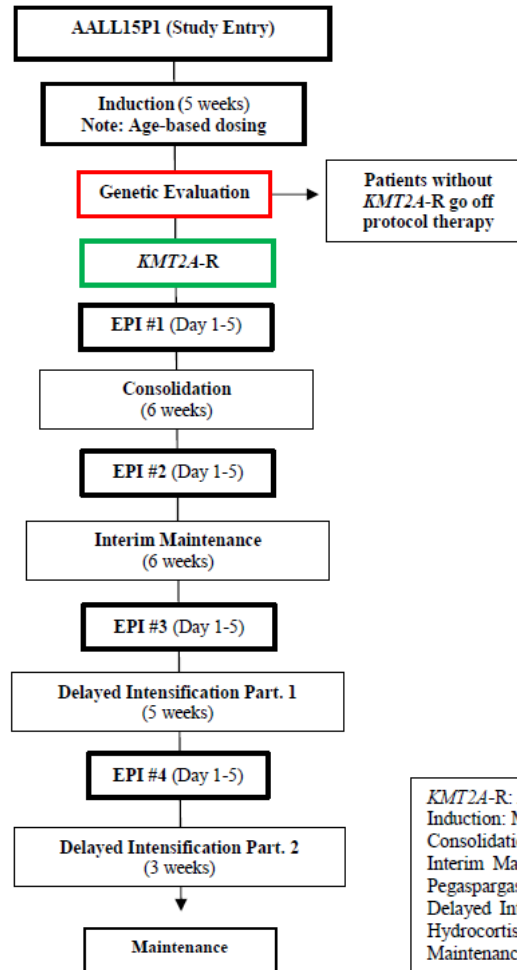
The rationale for this protocol was that low-dose azacitidine as an epigenetic priming agent could reverse aberrant DNA methylation, overcome drug resistance, and improve the cytotoxic effect of the chemotherapy medications (a pre-treatment).

Experimental Study Schema



KMT2A-R: *KMT2A* gene- Rearrangement EPI: Azacitidine Epigenetic Therapy
 Induction: Methotrexate, Predniso(lo)ne, Daunorubicin, Cytarabine, Dexamethasone, Vincristine, Pegaspargase, and Hydrocortisone
 Consolidation: Cyclophosphamide, Mesna, Mercaptopurine, Cytarabine, Methotrexate, and Hydrocortisone.
 Interim Maintenance: Mercaptopurine, High-dose Methotrexate, Leucovorin, Methotrexate/Hydrocortisone, High-dose Cytarabine, and Pegaspargase.
 Delayed Intensification: Dexamethasone, 6-Thioguanine, Vincristine, Daunorubicin, Pegaspargase, Cyclophosphamide, Cytarabine, and Hydrocortisone
 Maintenance: Mercaptopurine, Methotrexate, Hydrocortisone, and Cytarabine

Experimental Study Schema



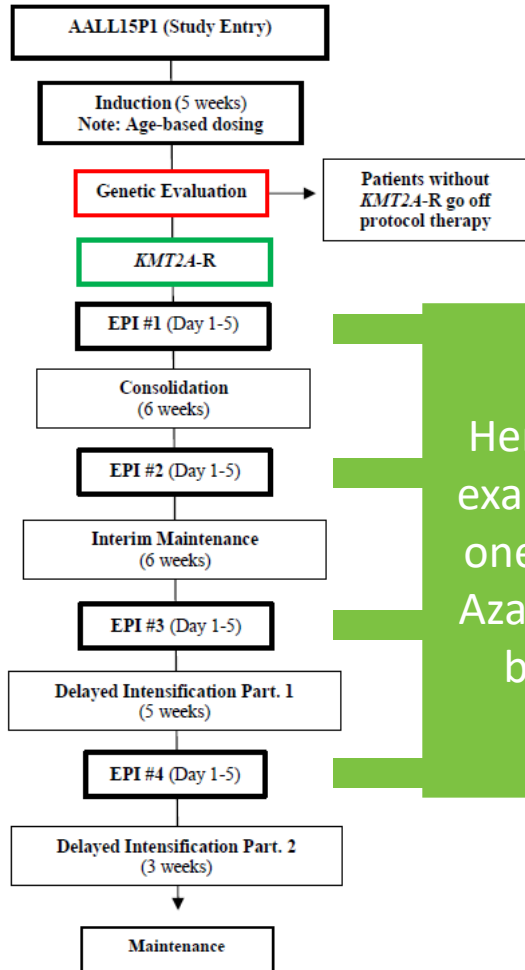
Patients without *KMT2A-R* go off protocol therapy

Begin each Azacitidine EPI Block when peripheral counts recover with ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$, and resolution of any toxicity.

Four cycles of Azacitidine given as a “priming agent” in the EPI blocks for the upcoming phase.

KMT2A-R: *KMT2A* gene- Rearrangement EPI: Azacitidine Epigenetic Therapy
 Induction: Methotrexate, Prednisolone, Daunorubicin, Cytarabine, Dexamethasone, Vincristine, Pegaspargase, and Hydrocortisone
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 Delayed Intensification: Dexamethasone, 6-Thioguanine, Vincristine, Daunorubicin, Pegaspargase, Cyclophosphamide, Cytarabine, and Hydrocortisone
 Maintenance: Mercaptopurine, Methotrexate, Hydrocortisone, and Cytarabine

Azacitidine



Here is an example of one of the Azacitidine blocks

CHILDREN'S ONCOLOGY GROUP THIS PROTOCOL IS FOR RESEARCH PURPOSES ONLY, SEE PAGE 1 FOR USAGE POLICY AALL15P1 Page 1 of 2

4.3 Azacitidine EPI BLOCK #1

4.3.1 Therapy Delivery Map – Azacitidine EPI BLOCK #1
 Following Induction therapy and the recovery of peripheral blood cell counts, azacitidine will be administered as a pre-treatment prior to Consolidation therapy, for 5 days. Azacitidine therapy is 5 days.

Patient COG ID number _____ DOB _____

Patients with *KMT2A-R* M3 marrow, start EPI Block #1 immediately following the completion of Induction therapy. Patients with *KMT2A-R* M1 or M2 marrow, start EPI Block #1 when ANC \geq 500/ μ L and platelets \geq 50,000/ μ L, and resolution of mucositis and/or diaper area dermatitis to \leq Grade 2 (whichever occurs later). Treatment details and criteria to start are in [Section 4.3.3](#). This Therapy Delivery Map is two (2) pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Azacitidine (AZA) IND# 133688	IV over 10-40 mins	2.5 mg/kg/dose	1-5	Note: Infusion must be completed within 45 minutes of vial reconstitution.

Ht _____ cm Wt _____ kg BSA _____ m²

Date Due	Date Given	Day	Azacitidine _____ mg	Studies
Enter actual dose administered below				
		1	_____ mg	a-d
		2	_____ mg	
		3	_____ mg	e
		4	_____ mg	e
		5	_____ mg	d-e
		6	Continue to Consolidation (Section 4.4) on Day 6 irrespective of ANC and platelet counts.	

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IV](#) and the COG Member website for Supportive Care Guidelines.

Since this is a study drug, it will be given at the tertiary centres only

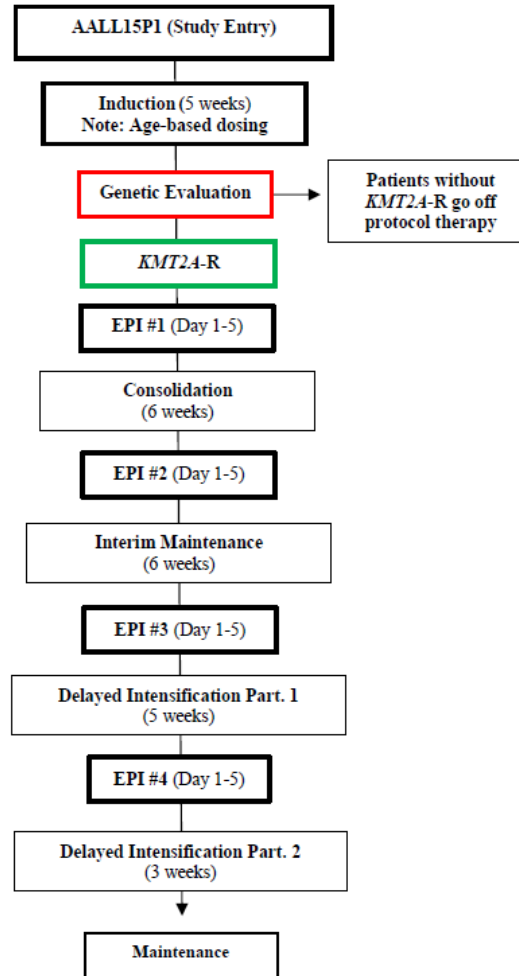
Azacitidine:
Intravenous (IV) over 10-40 mins
 Days: 1-5
 Dose: 2.5 mg/kg/dose
 Note: Infusion must be completed within 45 minutes of vial reconstitution

Azacitidine: Dose Modifications

Dose-Limiting Toxicity (DLT) evaluation period consists of the first three courses of azacitidine in combination with chemotherapy (EPI#1 through DI Part 1) and until the patient meets counts requirements to begin the fourth course of azacitidine (EPI #4).

During the evaluation period, the patient will be seen at the tertiary centre. If a patient who is having toxicity symptoms arrives at your centre for assessment, please contact the tertiary team for guidance and possible transfer.

Experimental Study Schema



Consolidation

4.4.1 Therapy Delivery Map - CONSOLIDATION

All patients will receive the same Consolidation therapy with regards to agents and schedule. Non-IT drugs are dosed based on age on Day 1 of Consolidation and BSA, as outlined below. IT doses are based on age on the day of administration. Consolidation therapy is 6 weeks (42 days) duration.

Patient COG ID Number _____ DOB _____

Following completion of Azacitidine Block 1 (EPI#1), begin Consolidation therapy on Day 6 irrespective of peripheral blood cell counts. Details and criteria to start are in [Section 4.4.3](#). This Therapy Delivery Map is two (2) pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES								
Cyclophosphamide (CPM)	IV over 30-60 min	<table border="1"> <tr><th>Age</th><th>Dose</th></tr> <tr><td>< 6 mo</td><td>670 mg/m²/dose</td></tr> <tr><td>≥ 6 mo & < 12 mo</td><td>750 mg/m²/dose</td></tr> <tr><td>≥ 12 mo</td><td>1000 mg/m²/dose</td></tr> </table>	Age	Dose	< 6 mo	670 mg/m ² /dose	≥ 6 mo & < 12 mo	750 mg/m ² /dose	≥ 12 mo	1000 mg/m ² /dose	1 & 29	Must have ANC ≥ 500/μL and platelets ≥ 30,000/μL to receive Day 29 CPM. Refer to Section 4.4.3 for admin guidelines.
Age	Dose											
< 6 mo	670 mg/m ² /dose											
≥ 6 mo & < 12 mo	750 mg/m ² /dose											
≥ 12 mo	1000 mg/m ² /dose											
Mesna	IV over 15min	<table border="1"> <tr><th>Age</th><th>Dose</th></tr> <tr><td>< 6 mo</td><td>134 mg/m²/dose</td></tr> <tr><td>≥ 6 mo & < 12 mo</td><td>150 mg/m²/dose</td></tr> <tr><td>≥ 12 mo</td><td>200 mg/m²/dose</td></tr> </table>	Age	Dose	< 6 mo	134 mg/m ² /dose	≥ 6 mo & < 12 mo	150 mg/m ² /dose	≥ 12 mo	200 mg/m ² /dose	1 & 29	Administer at 0, 4 and 8 hours from the start of CPM infusion. Refer to Section 4.4.3 for admin guidelines.
Age	Dose											
< 6 mo	134 mg/m ² /dose											
≥ 6 mo & < 12 mo	150 mg/m ² /dose											
≥ 12 mo	200 mg/m ² /dose											
Mercaptopurine (MP)	PO or NG	<table border="1"> <tr><th>Age</th><th>Dose</th></tr> <tr><td>< 6 mo</td><td>40 mg/m²/dose</td></tr> <tr><td>≥ 6 mo & < 12 mo</td><td>45 mg/m²/dose</td></tr> <tr><td>≥ 12 mo</td><td>60 mg/m²/dose</td></tr> </table>	Age	Dose	< 6 mo	40 mg/m ² /dose	≥ 6 mo & < 12 mo	45 mg/m ² /dose	≥ 12 mo	60 mg/m ² /dose	1-28	Refer to Section 4.4.3 and Section 5.7 for admin guidelines.
Age	Dose											
< 6 mo	40 mg/m ² /dose											
≥ 6 mo & < 12 mo	45 mg/m ² /dose											
≥ 12 mo	60 mg/m ² /dose											
Cytarabine (ARAC)	IV push or SubQ	<table border="1"> <tr><th>Age</th><th>Dose</th></tr> <tr><td>< 6 mo</td><td>50 mg/m²/dose</td></tr> <tr><td>≥ 6 mo & < 12 mo</td><td>56 mg/m²/dose</td></tr> <tr><td>≥ 12 mo</td><td>75 mg/m²/dose</td></tr> </table>	Age	Dose	< 6 mo	50 mg/m ² /dose	≥ 6 mo & < 12 mo	56 mg/m ² /dose	≥ 12 mo	75 mg/m ² /dose	3-6, 10-13, 17-20, & 24-27	Refer to Section 4.4.3 for admin guidelines.
Age	Dose											
< 6 mo	50 mg/m ² /dose											
≥ 6 mo & < 12 mo	56 mg/m ² /dose											
≥ 12 mo	75 mg/m ² /dose											
Cytarabine (IT ARAC)	IT	<table border="1"> <tr><th>Age (yr)</th><th>Dose</th></tr> <tr><td>< 1</td><td>15 mg</td></tr> <tr><td>≥ 1</td><td>20 mg</td></tr> </table>	Age (yr)	Dose	< 1	15 mg	≥ 1	20 mg	10			
Age (yr)	Dose											
< 1	15 mg											
≥ 1	20 mg											
Intrathecal Hydrocortisone (IT HC)	IT	<table border="1"> <tr><th>Age (yr)</th><th>Dose</th></tr> <tr><td>< 1</td><td>12 mg</td></tr> <tr><td>≥ 1</td><td>16 mg</td></tr> </table>	Age (yr)	Dose	< 1	12 mg	≥ 1	16 mg	10 & 24			
Age (yr)	Dose											
< 1	12 mg											
≥ 1	16 mg											
Intrathecal Methotrexate (IT MTX)	IT	<table border="1"> <tr><th>Age (yr)</th><th>Dose</th></tr> <tr><td>< 1</td><td>6 mg</td></tr> <tr><td>≥ 1</td><td>8 mg</td></tr> </table>	Age (yr)	Dose	< 1	6 mg	≥ 1	8 mg	24			
Age (yr)	Dose											
< 1	6 mg											
≥ 1	8 mg											

More total doses of Cytarabine in this study's Consolidation phase

Date Due	Date Given	Day	CPM mg	MESNA mg mg mg mg	MP mg	ARAC mg	IT ARAC mg	IT HC mg	IT MTX mg	Studies	
		1	_____ mg	_____ mg _____ mg _____ mg						b-c	
		3			_____ mg						
		4			_____ mg						
		5			_____ mg						
		6			_____ mg						
		10				_____ mg	_____ mg	_____ mg		b, d	
		11				_____ mg					
		12				_____ mg					
		13				_____ mg					
		17				_____ mg					
		18				_____ mg					
		19				_____ mg					
		20				_____ mg					
		24				_____ mg		_____ mg	_____ mg	b, d	
		25				_____ mg					
		26				_____ mg					
		27				_____ mg					
		28				_____ mg					
		29	_____ mg	_____ mg _____ mg _____ mg						a-c	
		42								b, e-g	
		43	If M1 marrow is achieved, continue to azacitidine EPI Block #2 (Section 4.5) on Day 43 or when ANC ≥ 500/μL and platelets ≥ 50,000/μL, and resolution of mucositis and diaper area dermatitis to ≤ Grade 2 (whichever occurs later).								

Consolidation

Sepsis is a concern for these patients due to:

- Increased numbers of myelosuppressive agents during the consolidation phase
- These patients are infants!

Maintenance

Oral Chemo starting dose based on AGE on Day 1 of
Maintenance Cycle 1

<u>Mercaptopurine: Oral (PO) or Nasogastric (NG)</u>	
Days: Days 1-84	
Dose: Age based dosing	
<u>Age</u>	<u>Dose</u>
≥ 6 mo & < 12 mo	38 mg/m ² /dose
≥ 12 mo	50 mg/m ² /dose

<u>Methotrexate: Oral (PO)</u>	
Days: Once weekly, omit during week 1.	
Dose: Aged based dosing	
<u>Age</u>	<u>Dose</u>
≥ 6 mo & < 12 mo	15 mg/m ² /dose
≥ 12 mo	20 mg/m ² /dose

Dose escalation in Maintenance based on ANC

Summary

To be enrolled on this study, the patient must have a KMT2A gene rearrangement

To evaluate the tolerability of azacitidine in addition to Interfant-06 standard chemotherapy in infants

Azacitidine is used as an epigenetic priming agent that could reverse aberrant DNA methylation, overcome drug resistance, and improve the cytotoxic effect of the chemotherapy medications

In the Maintenance phase, the starting dose is based on the patient's age at the start of the cycle!

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