

Outstanding outcomes in infants with *KMT2A*-germline acute lymphoblastic leukemia treated with chemotherapy alone: results of the Children's Oncology Group AALL0631 trial

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SUPPLEMENTAL TABLES

Table S1 Treatment details for infants with *KMT2A*-g leukemia

	Route	Dose	Day(s) of phase
Cohort 2 Induction (5 weeks)			
Prednisone (or methylprednisolone IV at 80% of the prednisone dose)	PO div TID	Age ≥6 months, 45 mg/m ² /day Age ≥7 days to <6 months, 40 mg/m ² /day Age <7 days, 30 mg/m ² /day	1-7
Dexamethasone	IV or PO div TID	Age ≥6 months, 4.5 mg/m ² /day Age ≥7 days to <6 months, 4 mg/m ² /day Age <7 days, 3 mg/m ² /day	8-28
Vincristine	IV push	Age ≥6 months, 1.125 mg/m ² Age ≥7 days to <6 months, 1 mg/m ² Age <7 days, 0.75 mg/m ²	8, 15, 22, 29
Daunorubicin	IV over 30 min	Age ≥6 months, 22.5 mg/m ² Age ≥7 days to <6 months, 20 mg/m ² Age <7 days, 15 mg/m ²	8, 9
<i>E. coli</i> L-Asparaginase (or <i>Erwinia</i> L-asparaginase)	IM	Age ≥6 months, 7500 IU/m ² (or <i>Erwinia</i> , 30,000 IU/m ²) Age ≥7 days to <6 months, 6675 IU/m ² (or <i>Erwinia</i> , 27,000 IU/m ²) Age <7 days, 5000 IU/m ² (or <i>Erwinia</i> , 20,000 IU/m ²)	15, 18, 22, 25, 29, 33
Cytarabine	IV over 30 min	Age ≥6 months, 56.25 mg/m ² Age ≥7 days to <6 months, 50 mg/m ² Age <7 days, 37.5 mg/m ²	8-21
Methotrexate (MTX)	IT	Age <1 year, 6 mg Age ≥1 year, 8 mg	1, 29
Cytarabine (ARAC)	IT	Age <1 year, 15 mg Age ≥1 year, 20 mg	15
Hydrocortisone (HC)	IT	Age <1 year, 12 mg Age ≥1 year, 16 mg	15, 29
Induction Intensification (4 weeks)			
High dose methotrexate	IV over 24 hours	4000 mg/m ²	1, 8
Triple intrathecal therapy	IT	Age <1 year, MTX 7.5 mg, ARAC 15 mg, HC 7.5 mg Age ≥1 year, MTX 8 mg, ARAC 16 mg, HC 8 mg Delivered within 6 hours of start of IV methotrexate	1, 8

Leucovorin rescue	IV or PO	15 mg/m ² at hours 42, 48 after start of IV methotrexate	2, 9
Etoposide	IV over 2 hrs	100 mg/m ²	15-19
Cyclophosphamide	IV over 30 min	300 mg/m ²	15-19
Mesna	IV over 30 min followed by CI	150 mg/m ² with cyclophosphamide and as a 4-hour continuous infusion following cyclophosphamide, 2 doses per day	15-19
Filgrastim	SQ or IV	5 mcg/kg/dose daily until ANC >1500/μL x 2 days post nadir	Beginning on day 20
Re-Induction (3 weeks)			
Vincristine	IV push	0.05 mg/kg 0.03 mg/kg	1, 15 8
Daunorubicin	IV over 30 min	Age <6 months, 1.7 mg/kg Age ≥6 to <9 months, 2.1 mg/kg Age ≥9 months, 2.6 mg/kg	1, 2
Cyclophosphamide	IV over 30 min	250 mg/m ² every 12 hours	3, 4
Mesna	IV over 30 min followed by CI	125 mg/m ² with cyclophosphamide and as a 4-hour continuous infusion following cyclophosphamide, 4 doses per day	3, 4
Pegaspargase	IM	2500 IU/m ²	4
Dexamethasone	PO or IV	5 mg/m ² /dose BID	1-7 and 15-21
Triple intrathecal therapy	IT	Age <1 year, MTX 7.5 mg, ARAC 15 mg, HC 7.5 mg Age ≥1 year, MTX 8 mg, ARAC 16 mg, HC 8 mg	1, 15
Filgrastim	SQ or IV	5 mcg/kg daily until ANC >1500/μL x 2 days post nadir	Beginning on day 5
Consolidation (7 weeks)			
Repeat Days 1-19 of Induction Intensification			1-19
Filgrastim	SQ or IV	5 mcg/kg/dose daily until ANC >1500/μL x 2 days post nadir	Beginning on days 20 and 31
High dose cytarabine	IV over 3 hrs	3000 mg/m ² every 12 hours	29, 30
Pegaspargase	IM	2500 IU/m ² administered 3 hours after final high dose cytarabine	30
Continuation I (2 cycles, 11 weeks each)			
Vincristine	IV push	0.05 mg/kg	1, 29
Dexamethasone	PO or IV	3 mg/m ² /dose BID	1-5 and 29-33
Triple intrathecal therapy	IT	Age <1 year, MTX 7.5 mg, ARAC 15 mg, HC 7.5 mg Age ≥1 year, MTX 8 mg, ARAC 16 mg, HC 8 mg	1, 29
Methotrexate	IV push	20 mg/m ²	8, 15, 22, 36, 43, 50
Mercaptopurine	PO	75 mg/m ²	8-28 and 36-56
Etoposide	IV over 2 hrs	100 mg/m ²	57-61
Cyclophosphamide	IV over 30 min	300 mg/m ²	57-61

Mesna	IV over 30 min followed by CI	150 mg/m ² with cyclophosphamide and as a 4-hour continuous infusion following cyclophosphamide, 2 doses per day	57-61
Filgrastim	SQ or IV	5 mcg/kg/dose daily until ANC >1500/μL x 2 days post nadir	Beginning on day 62
Continuation II (12 week cycles repeated until 2 years from diagnosis)			
Vincristine	IV push	0.05 mg/kg	1, 29, 57
Dexamethasone	PO or IV	3 mg/m ² /dose BID	1-5, 29-33, 57-61
Methotrexate	IT	Age <1 year, 7.5 mg Age ≥1 to <2 years, 8 mg Age ≥2 years, 10 mg	1
Methotrexate	PO	20 mg/m ²	8, 15, 22, 36, 43, 50, 64, 71, 78
Mercaptopurine	PO	75 mg/m ²	8-28, 36-56, 64-84

Abbreviations: *KMT2A*-g, *KMT2A*-germline; IV, intravenous; IT, intrathecal; MTX, methotrexate; ARAC, cytarabine; HC, hydrocortisone; PO, by mouth; div, divided; mg, milligram; TID, three times daily; min, minutes; IM, intramuscular; IU, international units; hrs, hours; CI, continuous infusion; SQ, sub-cutaneous; mcg, microgram; kg, kilogram; ANC, absolute neutrophil count; BID, twice daily

Table S2. Complete karyotypes for *KMT2A*-g cases with available cytogenetic data

Patient	Age at diagnosis	Diagnosis	WBC count at diagnosis	Karyotype
Abnormal chromosome 9p				
1	160 days	B-ALL	94.9	45,XY,dic(9;20)(p13;q11.2)[19]/46,XY[2]
2	174 days	B-ALL	2.4	45,XX,dic(9;17)(p13;p11.2)[5]/46,XX[10]
3	200 days	B-ALL	2.8	46,XY,add(7)(p13),der(9)t(9;10)(p13;p13),der(9)t(9;10)(p13;q24),der(10)t(9;10)(p13;p13)t(9;10)(p13;q24)[14]/46,XY[6]
4	268 days	B-ALL	212.3	46,XY,add(9)(p22),-11,der(11)t(9;11)(p13;p11.2)ins(11;?)(p11.2;?),+del(15)(q22q24),der(15)(15pter->15q24::11q23->11q13::9p22->9pter)[17]/46,XY[3]
5	299 days	B-ALL	21.6	45,XY,dic(9;20)(p13;q11.2)[13]/46,XY[7]
6	322 days	B-ALL	143.5	46,XY,r(4)(p16q35),del(9)(p13),rea(12)[7]/46,XY[16]
7	331 days	B-ALL	14.5	46,XX,t(1;7)(q21;p22),dic(9;20)(p13;q11.2),+21[15]/46,sl,del(6)(q11.2q22.31)[2]/46,XX[2]
8	331 days	B-ALL	89.9	45,XX,dic(9;20)(p13;q11.2)[4]/46,XX[36]
9	333 days	B-ALL	520.4	45,XX,dic(9;20)(p13;q11.2)[20]
10	349 days	B-ALL	140	46,X,t(X;7;9;1)(q22;q22;p24;p13)[17]/46,XX[3]
t(1;19)(q23;p13.3) or 19p13 variant				
11	252 days	B-ALL	51	46,XX,t(1;19)(q23;p13.3)[9]/46,XX[16]
12	307 days	B-ALL	68.9	46,XX,der(19)t(1;19)(q23;p13.3)[4]/46,XX[16]
13	308 days	B-ALL	10.2	46,XX,add(19)(p13.3)[8]/46,XX[11]

14	338 days	B-ALL	134.7	47,XX,t(1;19)(q23;p13.3),+6[cp6]/46,XX[14]
15	363 days	B-ALL	58.3	46,XY,der(19)t(1;19)(q23;p13)[7]/46,XY[13]
Hyperdiploid (>51 chromosomes)				
16	292 days	B-ALL	38.8	55,XX,+X,+4,+6,+8,+14,+17,+18,+21,+21[16]/46,XX[6]
17	313 days	B-ALL	168	54,XY,+X,+Y,+4,+6,+17,+18,+18,+21[cp4]/46,XY[16]
18	351 days	B-ALL	6	53,XX,+X,+4,+6,+10,+18,+21,+21[2]/54,sl,+9[1]/54,sl,i(7)(q10),+9[6]/46,XX[11]
Abnormal <i>TRA</i> (14q11.2) or <i>TRB</i> (7q34) locus				
19	322 days	T-ALL	918.2	46,XY,t(6;7)(q23;q34)[14]/46,XY[6]
20	360 days	T-ALL	405.3	46,XX,t(7;14)(p13;q11.2),der(9)(9qter->9q13::9p13->9qter)[15]/46,XX[5]
t(12;21)(p13;q22) or variant				
21	360 days	B-ALL	67.8	46,XY,ins(21;12)(q22;p13p13)/47,sl,+mar[4]/46,XY
Abnormal, other				
22	54 days	B-ALL	43	46,X,t(X;10;14)(p21.2;p12.2;q24)[16]/46,XX[30]
23	128 days	T-ALL	445.5	46,X,t(X;11)(q25;p13)[20]
24	139 days	B-ALL	27.5	46,XY,t(5;15)(p15.3;q13)[4]/46,XY[16]
25	153 days	B-ALL	25	46,XX,del(6)(q13q21)[5]/46,XX[15]
26	199 days	B-ALL	193.4	46,XX,i(1)(q10)[12]/46,XX[10]
27	206 days	B-ALL	43.9	46,XY,t(7;15)(q22;q15)[9]/46,XY[11]
28	226 days	B-ALL	103.8	46,XX,add(3)(q25),?dup(8)(q21.1q21.3),der(12)del(12)(p11.2p12)t(12;15)(q13;q22),der(15)t(12;15)[20]

29	250 days	B-ALL	29.76	46,XY,t(2;7)(p11.2;p15)[11]/46,XY[9]
30	261 days	B-ALL	9.8	46,XX,del(9)(q13q22),der(21)t(21;21)(p11.2;q22)[3]/46,XX[17]
31	277 days	B-ALL	156.4	46,XX,i(8)(q10)[12]47,XX,+8[4]/46,XX[4]
32	282 days	B-ALL	10.7	46,XX,t(5;15)(p15;q11.2)[10]/46,XX[10]
33	288 days	B-ALL	229	45,XX,der(7;12)dic(7;12)(p11.1;p11.1)inv(12)(p13.3q24.3)[8]/46,XX[12]
34	309 days	B-ALL	29.6	46,XY,t(3;15;8)(p12;q13;p11.2)[15]/46,XY[5]
35	331 days	B-ALL	10.6	47,XY,+10[17]/48,sl,+X[2]/46,XY[3]
36	363 days	B-ALL	21	44,XX,del(3)(p21),-5,add(6)(p21.3),add(6)(p25),-7,add(8)(p23),del(13)(q14q22),add(14)(q21),-15,-19,+21,dic(21;22)(p11.2;p11.2),+22,der(22)(14qter->14q21::??::22p11.2->22qter),+mar[cp3]/45,sl,+10[cp6]/46,XX[15]
Normal diploid				
37	78 days	B-ALL	78.9	46,XY[20]
38	97 days	B-ALL	84.8	46,XX[20]
39	122 days	B-ALL	29.7	46,XX[20]
40	135 days	B-ALL	2.6	46,XY[20]
41	163 days	B-ALL	10	46,XX[20]
42	201 days	B-ALL	11.6	46,XX[20]
43	221 days	B-ALL	29.7	46,XX[20]
44	245 days	B-ALL	15.8	46,XY[20]
45	255 days	B-ALL	5	46,XY[24]
46	261 days	T-ALL	24.6	46,XX[30]

47	295 days	B-ALL	620.1	46,XY[22]
48	313 days	B-ALL	0.6	46,XY[23]
49	315 days	B-ALL	9.9	46,XX[44]
50	325 days	B-ALL	10	46,XX[21]
51	329 days	T-ALL	620	46,XX[20]
52	342 days	B-ALL	32.9	46,XY[20]
53	355 days	T-ALL	375.2	46,XY[20]

Abbreviations: *KMT2A*-g, *KMT2A*-germline; WBC, white blood cell; B-ALL, B-acute lymphoblastic leukemia; T-ALL, T-acute lymphoblastic leukemia; *TRA*, T cell Receptor Alpha; *TRB*, T cell Receptor

Beta

Table S3. Grade 3 and 4 toxicities reported for infants with *KMT2A*-g leukemia

	Induction	Induction Intensification	Reinduction	Consolidation	Continuation I	Continuation II	All Reporting Periods
	N=64	N=60	N=60	N=60	N=57	N=56	N=64
Infectious	21 (33%)	15 (25%)	12 (20%)	22 (37%)	25 (44%)	23 (41%)	48 (75%)
Gastrointestinal	15 (23%)	31 (52%)	6 (10%)	18 (30%)	7 (12%)	4 (7%)	48 (75%)
Metabolism/Nutrition	23 (36%)	20 (33%)	13 (22%)	15 (25%)	11 (19%)	9 (16%)	39 (61%)
Nervous	1 (2%)	--	--	--	1 (2%)	2 (4%)	3 (5%)
Respiratory	4 (6%)	4 (7%)	--	2 (3%)	3 (5%)	3 (5%)	11 (17%)
Skin/Subcutaneous	6 (9%)	5 (8%)	3 (5%)	4 (7%)	--	1 (2%)	17 (27%)
Cardiac	1 (2%)	1 (2%)	--	--	1 (2%)	--	2 (3%)
Vascular	9 (14%)	1 (2%)	1 (2%)	--	1 (2%)	--	10 (16%)
Hematologic							
Neutropenia	18 (28%)	8 (13%)	9 (15%)	10 (17%)	17 (30%)	8 (14%)	35 (55%)
Thrombocytopenia	1 (2%)	1 (2%)	2 (3%)	4 (7%)	3 (5%)	1 (2%)	10 (16%)

Abbreviations: *KMT2A*-g, *KMT2A*-germline