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Presentation and management of pediatric T-cell acute lymphoblastic leukemia with mediastinal mass and hyperleukocytosis

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BM, ZH, and HI contributed to the study conception and design. BM, AR, ZH, and HI collected and verified the accuracy of the data. YS, CC, and LT performed statistical analysis. BM, YS, ZH, AH, LT, SJ, CHP, and HI drafted and revised the manuscript. All authors have read and approved the final manuscript for submission.

T-cell acute lymphoblastic leukemia (T-ALL) accounts for approximately 15% of newly diagnosed pediatric ALL cases, and its outcomes have markedly improved.[1, 2] Life-threatening presentations of T-ALL, including mediastinal mass, hyperleukocytosis (leukocyte count ≥ 100×10^9/L), and tumor lysis syndrome (TLS), can affect initial care, including diagnostic sampling (e.g., bone marrow, cerebrospinal fluid), sedation strategy, venous access, cytoreduction, and therapy initiation.[3-6] We retrospectively evaluated the impact of these life-threatening presentations on the initial management and outcomes in pediatric patients with T-ALL treated on Total Therapy Study XV (NCT00137111) or XVI (NCT00549848) at St. Jude Children's Research Hospital between 2000 and 2017.[7, 8] The study was approved by the institutional review board at St. Jude. Written informed consent was obtained from the parents, guardians, or patients, with assent from patients, as appropriate. The study was conducted in accordance with the Declaration of Helsinki.

We reviewed clinical and biological features, including sex, age at diagnosis, race (White, Black, other), presenting leukocyte count, central nervous system (CNS) involvement, immunophenotyping, and chest X-ray (CXR) findings at diagnosis.[4] To evaluate the delays in care, we calculated the time (in days) from the first complete blood count (CBC) to the procedures or initiation of protocol-defined therapy. TLS was diagnosed according to Cairo–Bishop criteria.[9] Its management included use of urate oxidase (rasburicase), allopurinol, phosphate binders, and dialysis. Coagulopathy was defined by the presence of at least two of the following: fibrinogen ≤ 100 mg/dL, international normalized ratio (INR) ≥ 2.0, and activated partial thromboplastin time (aPTT) ≥ 40 seconds. Treatment response with measurable residual disease (MRD) was evaluated by flow cytometry. Toxicities of interest included grade 3 or 4 hemorrhagic, neurologic, gastrointestinal/hepatic, cardiovascular (including thrombosis), metabolic, infectious, and pulmonary complications and death occurring within 14 days after the first CBC. Data on clinical management were collected, including intensive care unit (ICU) admissions (based on clinical need determined by treating physician, e.g., respiratory

compromise or significant metabolic derangements), types of anesthesia administered (local anesthesia only, intravenous [IV] sedation with fentanyl and/or ketamine, total IV anesthesia with propofol, with or without an opioid, and combined IV and inhalation anesthesia), respiratory support before and after diagnostic procedures (intubation [endotracheal intubation or laryngeal mask airway], minimally invasive support [face mask or nasal cannula], or no support), venous access (subcutaneous port-a-caths, temporary central lines [Hickman, femoral, and peripherally inserted central catheters], or peripheral lines), and cytoreduction strategies (including glucocorticoids [prednisone 40–60 mg/m^2/day, dexamethasone 6–10 mg/m^2/day, or methylprednisolone 20–30 mg/m^2/day] or leukapheresis determined by treating physician) used before initiating protocol therapies.

Associations between categorical variables were assessed using the chi-square test. Event-free survival (EFS); events defined as induction failure (MRD ≥ 5% at end of induction), relapse, death, or secondary malignancy; and overall survival (OS) were estimated using the Kaplan–Meier method, and comparisons were performed with the log-rank test. The cumulative incidence of refractory disease or relapse (CIR) was estimated using the cumulative incidence function, accounting for competing risks (death and secondary malignancy), and comparisons were performed with Gray's test. All statistical tests were two-sided.

The clinical characteristics of this T-ALL cohort (n = 168) are summarized in Table 1. Ninety-four patients (56%) presented with a mediastinal mass. These patients were more likely than those without a mass to exhibit both non-pulmonary intrathoracic findings (e.g., airway obstruction, pleural thickening, and/or effusions, $P < 0.001$) and pulmonary findings (e.g., pleural infiltrates, pneumonias, and/or atelectasis, $P = 0.016$) on CXR, and they were also more likely to exhibit a cortical or thymic immunophenotype rather than a pre-cortical phenotype ($P = 0.005$) and less likely to have ETP ALL ($P = 0.001$), demonstrated better MRD responses on days 15–19 of induction therapy ($P = 0.029$), and were less likely to be stratified as high-risk ($P = 0.019$). Additionally, they were more likely to develop hyperphosphatemia ($P = 0.026$) and were more

frequently treated with rasburicase ($P = 0.042$) and phosphate binders ($P = 0.003$) than were those without a mass (Table 2). For the initial management, ICU-level care was required for 50 (53%) of the 94 patients with a mediastinal mass, compared with 21 (28%) of the 74 patients without a mass ($P = 0.001$). During procedural sedation, patients with a mass were rarely intubated and were less likely to receive combined IV and inhalational anesthesia ($P < 0.001$ for both). However, they required post-procedural respiratory support more frequently than those without a mass ($P = 0.028$). Temporary central venous catheters were more commonly placed in patients with a mediastinal mass, whereas subcutaneous port-a-caths were more frequently used in those patients without a mass ($P < 0.001$).

Sixty-six (39%) of the 168 patients with T-ALL presented with hyperleukocytosis (Table 1). These patients were more likely to be White ($P = 0.013$), have CNS involvement at diagnosis ($P = 0.027$), and display cortical or thymic T-cell immunophenotypes rather than pre-cortical immunophenotypes ($P < 0.001$) when compared with those without hyperleukocytosis. Laboratory TLS occurred in 64 patients with hyperleukocytosis (97%), a higher proportion than in those without hyperleukocytosis ($P = 0.006$) (Table 2). Patients with hyperleukocytosis also had higher rates of hyperkalemia, hyperphosphatemia, and hyperuricemia ($P \leq 0.02$ for all) and were more frequently treated with rasburicase ($P = 0.001$). Coagulopathy was also more common in patients with hyperleukocytosis ($P < 0.001$) because of elevated INR values ($P < 0.001$) and hypofibrinogenemia ($P = 0.001$). Forty-three (65%) of the 66 patients with hyperleukocytosis required care in the ICU, compared with 28 patients (27%) without hyperleukocytosis ($P < 0.001$). Leukapheresis was exclusively used in patients with hyperleukocytosis (n = 8 [12%]; $P < 0.001$), all treated on Total XV. Patients with hyperleukocytosis were more likely than those without to forgo diagnostic bone marrow assessment ($P = 0.001$), with the diagnosis being established from peripheral blood samples instead, and they were less likely to experience delays in the initiation of protocol-mandated therapies ($P = 0.015$).

The 10-year EFS and OS for the 168 patients were 75.7% (95% CI: 68.4%–81.6%) and 84.0% (95% CI: 77.4%–88.9%), respectively, and the CIR at 10 years was 15.1% (95% CI: 10.1%–21%) (Table 3, Online Supplementary Figure S1A-C). EFS, OS, and CIR were significantly worse among patients with CNS involvement at diagnosis (which was also associated with isolated CNS relapse [Online Supplementary Table S1]), day 15–19 MRD ≥ 1%, and MRD ≥ 0.01% at the end of induction and among those stratified as high-risk as compared with standard-risk ($P \leq 0.036$ for all). Additionally, Black patients and patients of other non-White racial backgrounds experienced significantly worse EFS and OS when compared with White patients ($P \leq 0.031$ for both). OS was also significantly lower among female patients than among male patients ($P = 0.038$) and among patients with ETP ALL, as opposed to non-ETP subtypes ($P = 0.036$). Notably, the presence of a mediastinal mass or hyperleukocytosis had no significant impact on EFS, OS, CIR, or the incidence of adverse events (Tables 3, Online Supplementary Table S2, Online Supplementary Figure S1D-I). Importantly, no deaths were attributed to a mediastinal mass or hyperleukocytosis during the study period.

In our retrospective study of 168 patients with T-ALL, 94 (56%) presented with a mediastinal mass and 66 (39%) with hyperleukocytosis. Laboratory TLS occurred in 149 patients (89%). These oncologic emergencies necessitated prompt and individualized initial management, including ICU admission, anesthesia and procedural planning, aggressive TLS management, and cytoreduction. More than half of the patients with a mediastinal mass required ICU admission, primarily to manage cardiorespiratory complications such as respiratory failure, superior vena cava syndrome, pericardial or pleural effusions, and TLS. To mitigate this risk, patients with a mediastinal mass more frequently received less invasive approaches, including IV sedation or local anesthesia, to avoid intubation and obtain temporary central venous access. However, a higher proportion of the patients with a mediastinal mass required post-procedural respiratory support until the mass and the associated thoracic pathologies, such as pleural and pericardial effusions and pulmonary opacity, had improved.

Hyperleukocytosis carries risks of leukostasis, coagulopathy, and TLS (manifesting as hyperkalemia, hyperphosphatemia, and hyperuricemia), often necessitating ICU admission.[10] Consequently, these patients were more frequently treated with rasburicase, as recommended by clinical guidelines.[9, 11] We previously observed no clinical benefit of leukapheresis in children with ALL and leukocyte counts ≥ 200 × 10^9/L.[12] Instead, establishing the diagnosis via peripheral blood, using temporary central venous access, and a strategy of gradual cytoreduction with repeated doses of glucocorticoids, alongside close monitoring and supportive management of TLS, enabled earlier initiation of protocol-defined therapy than in patients without hyperleukocytosis.

Importantly, the presence of a mediastinal mass or hyperleukocytosis was not associated with inferior outcomes, incidences of adverse events, or early death. The favorable outcomes were achieved through a coordinated multidisciplinary approach emphasizing vigilant monitoring and proactive supportive care. As expected, established prognostic factors such as CNS involvement at diagnosis, suboptimal MRD responses, and high-risk stratification were all significantly associated with worse outcomes. Radiographic response of mediastinal masses during therapy was not systematically assessed, precluding evaluation of prognostic relevance. Recent genomic studies have refined the molecular classification of T-ALL and have demonstrated that such classifications correlate more strongly with outcomes than do immunophenotypic subtypes such as ETP ALL.[13-15] Further investigations of genetic alterations associated with mediastinal masses and hyperleukocytosis may offer additional insights into their clinical significance and underlying biology.

In summary, the initial management of newly diagnosed T-ALL requires a multidisciplinary and risk-adapted approach, as patients commonly present with critical features such as mediastinal mass, hyperleukocytosis, and TLS. With thoughtful procedural planning, robust supportive care and stepwise initiation of chemotherapy, early morbidity and mortality

associated with mediastinal mass or hyperleukocytosis were not observed, without inferior survival outcomes.

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Table 1. Presentation characteristics of all patients and those with a mediastinal mass or hyperleukocytosis.

Characteristics	All patients	Mediastinal mass			Hyperleukocytosis		
	Total No. of patients (%) n=168	No. of patients with mediastinal mass (%), n=94	No. of patients without mediastinal mass (%), n=74	*P*	No. of patients with hyperleukocytosis (%), n=66	No. of patients without hyperleukocytosis (%), n=102	*P*
Age, years							
≤ 10	97 (58)	59 (63)	38 (51)	0.133	36 (55)	61 (60)	0.776
> 10	71 (42)	35 (37)	36 (49)		30 (45)	41 (40)	
Sex							
Boys	118 (70)	66 (70)	52 (70)	0.994	48 (73)	70 (69)	0.570
Girls	50 (30)	28 (30)	22 (30)		18 (27)	32 (31)	
Self-declared race							
White	107 (64)	67 (71)	40 (54)	0.062	45 (68)	62 (61)	**0.013**
Black	39 (23)	17 (18)	22 (30)		14 (21)	25 (24)	
Other	22 (13)	10 (11)	12 (16)		7 (11)	15 (15)	
Leukocyte count, cells/μL							
<100,000	102 (61)	58 (62)	44 (59)	0.768		102 (100)	NA
≥100,000	66 (39)	36 (38)	30 (41)		66 (100)		
CNS leukemia at diagnosis							
No	84 (50)	49 (52)	35 (47)	0.534	26 (39)	58 (57)	**0.027**
Yes (CNS 2 and 3 and traumatic tap with blasts)	84 (50)	45 (48)	39 (53)		40 (61)	44 (43)	
St. Jude Total Therapy protocol							
Total XV	64 (38)	41 (44)	23 (31)	0.097	27 (41)	37 (36)	0.546
Total XVI	104 (62)	53 (56)	51 (69)		39 (59)	65 (64)	
CXR findings at diagnosis							
Non-pulmonary intrathoracic pathologies				**<0.001**			0.289
Yes	74 (44)	63 (67)	11 (15)		38 (58)	67 (66)	
No	94 (56)	31 (33)	63 (85)		28 (42)	35 (34)	
Pulmonary pathologies				**0.016**			0.151
Yes	32 (19)	24 (32)	8 (11)		9 (14)	23 (23)	
No	136 (81)	70 (68)	66 (89)		57 (86)	79 (77)	
Immunophenotypic classification of T cell maturation							
Pre-cortical	21 (12)	5 (5)	16 (22)	**0.005**	0 (0)	21 (21)	**<0.001**
Cortical	31 (19)	21 (23)	10 (13)		13 (20)	18 (18)	
Thymic	115 (69)	67 (72)	48 (65)		53 (80)	62 (62)	
No data	1	1				1	
Early T cell precursor							
Yes	19 (11)	4 (4)	15 (20)	**0.001**	4 (6)	15 (15)	0.084
No	149 (89)	90 (96)	59 (80)		62 (94)	87 (85)	
MRD at day 15-19 of induction, %							
<0.01%	45 (27)	33 (35)	12 (16)	**0.029**	19 (29)	26 (25)	0.372
≥0.01-0.99%	52 (31)	28 (30)	24 (32)		23 (35)	29 (28)	
≥1-4.99%	26 (16)	12 (13)	14 (19)		11 (17)	15 (15)	
≥5%	43 (26)	19 (20)	24 (32)		12 (18)	31 (30)	
No data	2	2			1	1	
MRD at end of induction, %							
<0.01%	125 (76)	72 (77)	53 (72)	0.460	48 (72)	77 (75)	0.910
≥0.01-0.99%	26 (16)	15 (16)	11 (15)		10 (15)	16 (16)	
≥1-4.99%	10 (6)	4 (4)	6 (8)		3 (5)	7 (7)	
≥5%	4 (2)	1 (1)	3 (4)		2 (3)	2 (2)	
No data	3	2	1		3		
Risk stratum							
Standard	136 (81)	82 (87)	54 (73)	**0.019**	57 (86)	79 (77)	0.151
High	32 (19)	12 (13)	20 (27)		9 (14)	23 (23)	

Abbreviations: CNS, central nervous system; CXR, chest X-ray; MRD, measurable residual disease; NA, not applicable

Table 2. Tumor lysis syndrome and management of patients with mediastinal mass or hyperleukocytosis

Characteristics	All patients	Mediastinal mass			Hyperleukocytosis		
	Total No. of patients (%) n=168	No. of patients with mediastinal mass (%), n=94	No. of patients without mediastinal mass (%), n=74	*P*	No. of patients with hyperleukocytosis (%), n=66	No. of patients without hyperleukocytosis (%), n=102	*P*
Laboratory tumor Lysis Syndrome							
Present	149 (89)	85 (90)	64 (86)	0.424	64 (97)	85 (83)	**0.006**
Absent	19 (11)	9 (10)	10 (14)		2 (3)	17 (17)	
Parameters for diagnosing laboratory tumor lysis syndrome							
Potassium				0.253			**0.001**
Yes	81 (48)	49 (52)	32 (43)		42 (64)	39 (38)	
No	87 (52)	45 (48)	42 (57)		24 (36)	63 (62)	
Phosphorus				**0.026**			**0.020**
Yes	115 (68)	71 (76)	44 (59)		52 (79)	63 (62)	
No	53 (32)	23 (24)	30 (41)		14 (21)	39 (38)	
Calcium				0.057			0.169
Yes	39 (23)	27 (29)	12 (16)		19 (29)	20 (20)	
No	129 (77)	67 (71)	62 (84)		47 (71)	82 (80)	
Uric acid				0.798			**0.001**
Yes	113 (67)	64 (68)	49 (66)		54 (82)	59 (58)	
No	55 (33)	30 (32)	25 (34)		12 (18)	43 (42)	
Parameters diagnosing clinical tumor lysis syndrome							
Creatinine				0.069			0.129
Yes	12 (7)	10 (11)	2 (3)		2 (3)	10 (10)	
No	156 (93)	84 (89)	72 (97)		64 (97)	92 (90)	
Seizure				0.441			0.393
Yes	1 (1)		1 (1)		1 (2)		
No	167 (99)	94 (100)	73 (99)		65 (98)	102 (100)	
Cardiac Arrhythmia				NA			NA
Yes	0						
No	168 (100)	94 (100)	74 (100)		66 (100)	102 (100)	
Coagulopathy							
Present at diagnosis				0.082			**<0.001**
Yes	25 (15)	10 (11)	15 (20)		19 (29)	6 (6)	
No	143 (85)	84 (89)	59 (80)		47 (71)	96 (94)	
INR ≥ 2 at diagnosis				0.427			**<0.001**
Yes	15 (9)	7 (7)	8 (11)		14 (21)	1 (1)	
No	150 (91)	86 (91)	64 (86)		52 (79)	98 (98)	
No data	3	1	2			3	
Fibrinogen ≤ 100 mg/dL				0.342			**0.001**
Yes	10 (6)	4 (4)	6 (8)		9 (14)	1 (1)	
No	152 (90)	86 (91)	66 (89)		56 (84)	96 (96)	
No data	6	4	2		1	5	
Management							
Rasburicase				**0.042**			**0.001**
Yes	118 (70)	72 (77)	46 (62)		56 (85)	62 (61)	
No	50 (30)	22 (23)	28 (38)		10 (15)	40 (39)	
Allopurinol				0.082			0.235
Yes	101 (60)	62 (66)	39 (53)		36 (55)	65 (64)	
No	67 (40)	32 (34)	35 (47)		30 (45)	47 (36)	
Phosphate binder				**0.003**			0.156
Yes	139 (83)	85 (90)	54 (73)		58 (88)	81 (79)	
No	29 (17)	9 (10)	20 (27)		8 (12)	21 (21)	
ICU admission							
Yes	71 (42)	50 (53)	21 (28)	**0.001**	43 (65)	28 (27)	**<0.001**
No	97 (58)	44 (47)	53 (72)		23 (35)	74 (73)	
Glucocorticoid cytoreduction							
Yes	70 (42)	39 (42)	31 (42)	0.958	30 (45)	40 (39)	0.423
No	98 (58)	55 (58)	43 (58)		36 (55)	82 (61)	
Venous Access							
Subcutaneous Port-a-cath	45 (27)	12 (13)	33 (45)	**<0.001**	9 (14)	36 (35)	**0.001**
Temporary lines (Hickman, PICC, or femoral)	118 (70)	79 (84)	39 (52)		52 (79)	66 (65)	
Peripheral line	5 (3)	3 (3)	2 (3)		5 (7)		
Procedural anesthesia							
Intravenous anesthesia with inhalational agent	56 (33)	18 (19)	38 (51)	**<0.001**	23 (35)	33 (32)	0.164
Total intravenous sedation	78 (46)	45 (48)	33 (45)		35 (53)	43 (42)	
Intravenous sedation or local anesthesia	34 (21)	31 (33)	3 (4)		8 (12)	26 (26)	
Procedural respiratory support							
Invasive (ET and LMA)	57 (34)	18 (19)	38 (51)	**<0.001**	23 (35)	34 (34)	0.982
Noninvasive (FM and NC) or no support	109 (65)	74 (79)	36 (49)		42 (64)	66 (65)	
No data	2 (1)	2 (2)			1 (1)	2 (2)	
Post-procedural respiratory support							
Yes (ET, FM, or NC)	33 (20)	24 (26)	9 (12)	**0.028**	16 (24)	17 (18)	0.209
No	134 (80)	69 (73)	65 (88)		49 (75)	85 (42)	
No data	1	1 (1)			1 (1)		
Diagnostic bone marrow assessment attained							
Yes	146 (87)	81 (86)	65 (88)	0.750	50 (76)	96 (94)	**0.001**
No	22 (13)	13 (14)	9 (12)		16 (24)	6 (6)	
Delay in protocol start							
Yes	133 (79)	75 (80)	58 (78)	0.823	46 (70)	87 (85)	**0.015**
No	35 (21)	19 (20)	16 (22)		20 (30)	15 (15)	

Abbreviations: INR, international normalized ratio; aPTT, activated partial thromboplastin time; ICU, intensive care unit; PICC, peripherally inserted central catheter; ET, endotracheal tube; LMA, laryngeal mask airway; FM, face mask; NC, nasal cannula

Table 3. Ten-year outcomes of patients with T-ALL based on clinical characteristics.

Characteristics	N (%)	10-year-EFS	*P*	10-year-OS	*P*	10-year-CIR	*P*
All patients							
	168	75.7% (95% CI: 68.4-81.6%)	NA	84% (95% CI: 77.4-88.9%)	NA	15.1% (95% CI: 10.1-21%)	NA
Age, years							
≤ 10	97 (58)	73.9% (95% CI: 63.8-81.6%)	0.561	84.5% (95% CI: 75.6-90.4%)	0.971	18.9% (95% CI: 11.7-27.4%)	0.121
> 10	71 (42)	78.4% (95% CI: 66.7-86.4%)		83.4% (95% CI: 71.8-90.5%)		9.9% (95% CI: 4.3-18.3%)	
Sex							
Boys	118 (70)	78.4% (95% CI: 69.7-84.9%)	0.241	87.7% (95% CI: 80.1-92.6%)	**0.038**	19% (95% CI: 12.4-26.6%)	0.788
Girls	50 (30)	69.1% (95% CI: 53.8-80.1%)		75.1% (95% CI: 60.3-85.1%)		16% (95% CI: 7.4-27.5%)	
Race							
White	107 (64)	82% (95% CI: 73.2-88.1%)	**0.018**	89.4% (95% CI: 81.6-94%)	**0.031**	13.3% (95% CI: 7.6-20.6%)	0.495
Black	39 (23)	69% (95% CI: 51.8-81%)		74% (95% CI: 57-85.1%)		20.7% (95% CI: 9.6-34.7%)	
Other	22 (13)	56.6% (95% CI: 32.7-74.8%)		75.6% (95% CI: 50.6-89.1%)		13.6% (95% CI: 3.3-31.4%)	
Mediastinal mass							
Yes	94 (56)	78.3% (95% CI: 68.3-85.4%)	0.450	85.7% (95% CI: 76.6-91.5%)	0.494	13.9% (95% CI: 7.8-21.8%)	0.644
No	74 (44)	72.5% (95% CI: 60.6-81.3%)		81.8% (95% CI: 70.5-89.1%)		16.7% (95% CI: 9.1-26.2%)	
Leukocyte count, cells/L							
$<100 \times 10^9$	102 (61)	78.2% (95% CI: 68.7-85.1%)	0.475	85.1% (95% CI: 76.4-90.7%)	0.744	12.7% (95% CI: 7.1-20%)	0.327
$\geq 100 \times 10^9$	66 (39)	72.1% (95% CI: 59.4-81.5%)		82.5% (95% CI: 70.5-90%)		18.6% (95% CI: 10.1-29%)	
CNS leukemia at diagnosis							
No	84 (50)	89.3% (95%CI: 80.4-94.3%)	**0.001**	92.9% (95% CI: 84.8-96.7%)	**0.003**	7.1% (95% CI: 2.9-14%)	**0.004**
Yes (CNS 2 and 3 and TLP with blasts)	84 (50)	61.9% (95%CI: 50.3-71.6%)		74.9% (95% CI: 63.6-83.1%)		23.2% (95% CI: 14.6-32.9%)	
CNS status at diagnosis							
CNS-1	84 (50)	89.3% (95% CI: 80.4-94.3%)	**0.001**	92.9% (95% CI: 84.8-96.7%)	**0.020**	7.1% (95% CI: 2.9-14%)	**0.036**
CNS-2	57 (34)	61.3% (95% CI: 46.7-73%)		74.9% (95% CI: 60.2-84.9%)		23.9% (95% CI: 13.4-36.2%)	
CNS-3	11 (7)	72.7% (95% CI: 37.1-90.3%)		81.8% (95% CI: 44.7-95.1%)		18.2% (95% CI: 2.4-45.7%)	
TLP with blasts	16 (9)	56.3% (95% CI: 29.5-76.2%)		68.8% (95% CI: 40.5-85.6%)		25% (95% CI: 7.3-48%)	
Immunophenotypic classification of T cell maturation							
Pre-cortical and Cortical	52 (31)	76.9% (95% CI: 63-86.2%)	0.963	88.5% (95% CI: 76.1-94.6%)	0.407	21.2% (95% CI: 11.2-33.2%)	0.118
Thymic	115 (69)	76% (95% CI: 66.9-82.9%)		82.8% (95% CI: 74.3-88.7%)		12.4% (95% CI: 7.1-19.3%)	
No data	1						
Early T cell precursor							
Yes	19 (11)	62.7% (95% CI: 37.2-80.2%)	0.129	68% (95% CI: 42.1-84.2%)	**0.036**	26.3% (95% CI: 9.2-47.4%)	0.125
No	149 (89)	77.4% (95% CI: 69.6-83.4%)		86% (95% CI: 79.1-90.8%)		13.7% (95% CI: 8.7-19.8%)	
MRD at day 15-19 of induction, %							
<1%	97 (58)	84% (95% CI: 74.8-90%)	**0.003**	92.2% (95% CI: 84.1-96.2%)	**0.001**	10.6% (95% CI: 5.4-17.9%)	**0.035**
≥1%	69 (42)	64.7% (95% CI: 52.1-74.8%)		73.4% (95% CI: 61.1-82.3%)		21.9% (95% CI: 12.9-32.3%)	
No data	2						
MRD at end of induction, %							
<0.01%	125 (76)	82.7% (95% CI: 74.6-88.4%)	**0.001**	88.2% (95% CI: 80.8-92.9%)	**0.035**	10.7% (95% CI: 6-17%)	**0.002**
≥0.01%	40 (24)	57.3% (95% CI: 40.5-70.9%)		74.8% (95% CI: 58.2-85.6%)		30% (95% CI: 16.6-44.6%)	
No data	3						
Risk stratum							
Standard	136 (81)	81.9% (95% CI: 74.1-87.5%)	**<0.001**	87.7% (95% CI: 80.6-92.3%)	**0.003**	10.5% (95% CI: 6-16.5%)	**<0.001**
High	32 (19)	49.8% (95% CI: 31.7-65.5%)		68.6% (95% CI: 49.5-81.7%)		34.4% (95% CI: 18.5-50.9%)	
Tumor lysis syndrome							
Present	149 (89)	76% (95% CI: 68.2-82.2%)	0.728	85.4% (95%CI: 78.4-90.2%)	0.109	15.7% (95% CI: 10.3-22.1%)	0.580
Absent	19 (11)	73.7% (95% CI: 47.9-88.1%)		73.7% (95%CI: 47.9-88.1%)		10.5% (95% CI: 1.6-29.1%)	
Coagulopathy present at diagnosis							
Yes	25 (15)	71.6% (95% CI: 49.4-85.3%)	0.574	83.5% (95% CI: 61.7-93.5%)	0.922	24.2% (95% CI: 9.6-42.4%)	0.143
No	143 (85)	76.4% (95% CI: 68.4-82.6%)		84.1% (95% CI: 76.8-89.2%)		13.5% (95% CI: 8.5-19.8%)	
ICU admission							
Yes	71 (42)	72.9% (95% CI: 60.9-81.8%)	0.437	84.2% (95% CI: 73.2-90.9%)	0.890	15.6% (95% CI: 8.2-25%)	0.801
No	97 (58)	77.8% (95% CI: 68-85%)		84% (95% CI: 74.7-90%)		14.7% (95% CI: 8.5-22.7%)	

Abbreviations: EFS, event-free survival; OS, overall survival; CIR, cumulative incidence of relapse; CI, confidence interval; CNS, central nervous system; TLP, traumatic lumbar puncture; MRD, measurable residual disease; ICU, intensive care unit

Supplemental Table 1. Cumulative incidence of isolated CNS relapse based on clinical characteristics

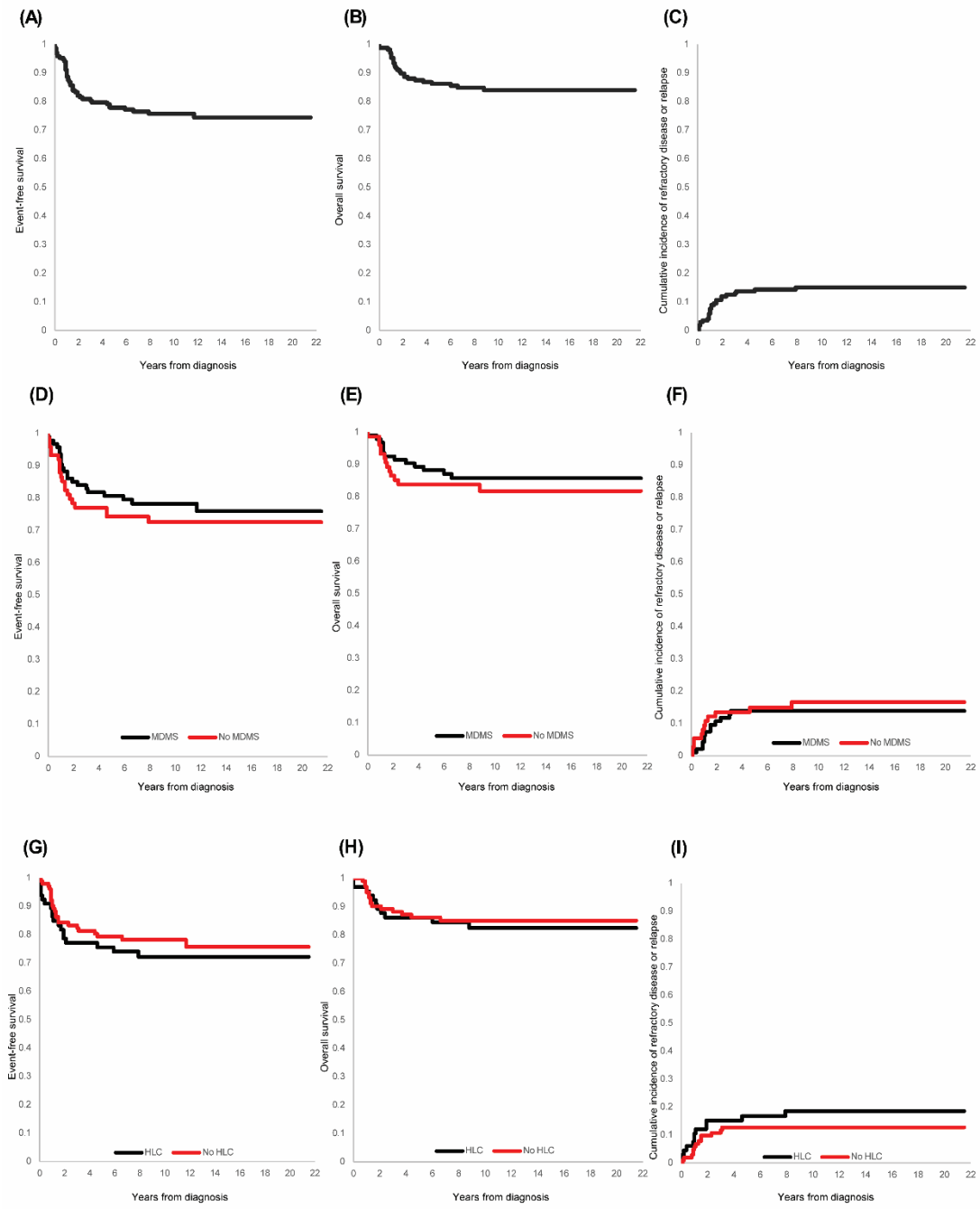
	N (%)	5-year-CIR	10-year-CIR	*P*
All patients				
	168	5.4% (95% CI: 2.6-9.6%)	5.4% (95% CI: 2.6-9.6%)	NA
Mediastinal mass				
Yes	94 (56)	6.4% (95% CI: 2.6-12.6%)	6.4% (95% CI: 2.6-12.6%)	0.500
No	74 (44)	4.1% (95% CI: 1.1-10.5%)	4.1% (95% CI: 1.1-10.5%)	
Leukocyte count at diagnosis				
$<100x10^9/L$	102 (61)	2.9% (95% CI: 0.8-7.7%)	2.9% (95% CI: 0.8-7.7%)	0.08
$\geq100x10^9/L$	66 (39)	9.1% (95% CI: 3.7-17.7%)	9.1% (95% CI: 3.7-17.7%)	
CNS leukemia at diagnosis				
No	84 (50)	1.2% (95% CI: 0.1-5.8%)	1.2% (95% CI: 0.1-5.8%)	**0.016**
Yes (CNS 2 and 3 and traumatic tap with blasts)	84 (50)	9.6% (95% CI: 4.5-17.1%)	9.6% (95% CI: 4.5-17.1%)	
CNS status at diagnosis				
CNS-1	84 (50)	1.2% (95% CI: 0.1-5.8%)	1.2% (95% CI: 0.1-5.8%)	0.098
CNS-2	57 (34)	10.7% (95% CI: 4.3-20.4%)	10.7% (95% CI: 4.3-20.4%)	
CNS-3	11 (7)	9.1% (95% CI: 0.4-35%)	9.1% (95% CI: 0.4-35%)	
Traumatic with blasts	16 (9)	6.3% (95% CI: 0.4-25.5%)	6.3% (95% CI: 0.4-25.5%)	

Abbreviations: CNS, central nervous system; CIR, cumulative incidence of relapse; CI, confidence interval; NA, not applicable

Supplemental Table 2. Adverse events within 14 days from diagnosis in patients with T-ALL based on clinical characteristics

Adverse effects	All patients	Mediastinal Mass			Hyperleukocytosis		
	Total No. of patients (%) n=168	No. of patients with mediastinal mass (%), n=94	No. of patients without mediastinal mass (%), n=74	*P*	No. of patients with hyperleukocytosis (%), n=66	No. of patients without hyperleukocytosis (%), n=102	*P*
Neurologic, n (%)	8 (8)	2 (4)	6 (11)	0.071	3 (6)	5 (9)	0.685
Pulmonary, n (%)	10 (9)	9 (18)	1 (2)		5 (10)	5 (9)	
Gastrointestinal/hepatic, n (%)	10 (9)	3 (6)	7 (13)		5 (10)	5 (9)	
Hemorrhagic/hematologic, n (%)	1 (1)	1 (2)	0		1 (2)	0	
Cardiovascular, n (%)	14 (13)	7 (14)	7 (13)		7 (14)	7 (13)	
Infection, n (%)	40 (38)	17 (33)	23 (42)		16 (31)	24 (44)	
Metabolic, n (%)	21 (20)	11 (22)	10 (18)		12 (24)	9 (16)	
Early death, n (%)	2 (2)	1 (2)	1 (2)		2 (4)	0	

Supplemental Figure 1.



Panels A-C show the event-free survival (EFS), overall survival (OS) and cumulative incidence of relapse or refractory disease (CIR) for all patients with T-cell acute lymphoblastic leukemia treated on St. Jude Total Therapy Studies XV and XVI. Panels D-F display the EFS, OS, and CIR stratified by the presence (black line) or absence (red line) of a mediastinal mass (MDMS). Panels G-I show the EFS, OS, and CIR stratified by the presence (black line) or absence (red line) of hyperleukocytosis (HLC).