ALL-253

Outcomes of Children With Down Syndrome and B-Cell Acute Lymphoblastic Leukemia Treated With a Reduced-Methotrexate Strategy in JCCG ALL-B12

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JCCG Japan Children's Cancer Group

INTRODUCTION

• Children with Down syndrome (DS) have a 10- to 20-fold increased risk of developing acute lymphoblastic leukemia (ALL) compared with the general pediatric population.[1,2]

• Although survival of DS-ALL has improved in recent trials, outcomes generally remain inferior to those of non-DS-ALL.[3]

AIM

• To assess prognosis, relapse patterns, and treatment-related toxicities of DS-ALL within the nationwide, risk-adapted JCCG ALL-B12 trial.

METHOD

• This study analyzed patients diagnosed with B-cell acute lymphoblastic leukemia (B-ALL) who were enrolled in the JCCG ALL-B12 trial between November 2012 and November 2017.[4,5]

• The ALL-B12 trial was a nationwide, multicenter clinical study conducted across 144 institutions in Japan.

• Risk was assigned as standard (SR), intermediate (IR), or high (HR) using protocol-defined clinical, genetic, and minimal residual disease (MRD) criteria.

• Treatment followed ALL-B12, and non-DS SR received reduced-intensity induction and 2 g/m² high-dose methotrexate (HD-MTX) in consolidation; IR received early intensification with augmented asparaginase and 5 g/m² HD-MTX; HR entered a randomized comparison between block-type consolidation and an HD-MTX regimen at 5 g/m² per cycle.

• DS-ALL received protocol-specified MTX modifications (0.5 g/m² for the first consolidation course, then 1.0 g/m²).

• Primary endpoints were 5-year event-free survival (EFS) and overall survival (OS), estimated using the Kaplan–Meier method and the log-rank test. Multivariable Cox models adjusted for age, protocol-defined risk group, and TP2 MRD. Grade ≥3 toxicities were graded by CTCAE v4.0 and summarized by treatment phase after allocation.

• The study was approved by the Certified Review Board of NHO Nagoya Medical Center and conducted in accordance with the Declaration of Helsinki.

CONCLUSIONS

In ALL-B12, DS status remained an independent adverse prognostic factor after adjustment for risk group and TP2 MRD. This adverse impact persisted even among patients with favorable TP2 MRD, highlighting the limits of current risk stratification. Although the reduced-methotrexate strategy appeared feasible, outcomes remained suboptimal, underscoring the need for DS-specific therapeutic strategies that improve antileukemic efficacy without compromising tolerability.

RESULTS

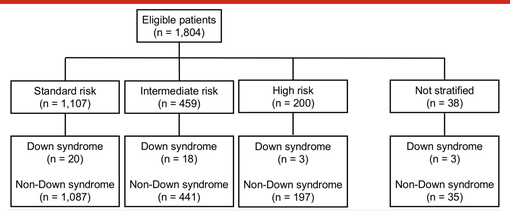

Figure 1. Distribution of eligible patients according to risk group and DS status.
A total of 1,804 eligible patients were included in the full analysis set and classified into risk groups (SR, IR, HR) based on predefined criteria. The diagram shows the distribution of DS-ALL and non-DS-ALL cases within each risk category.

Table 1. Baseline characteristics of patients with DS-ALL and non-DS-ALL.

	DS-ALL	Non-DS-ALL	P-value§
All	44 (100.0)	1,760 (100.0)	
Age, median (range)	7 (1-17)	4 (1-19)	< 0.01
Sex			1.00
Female	20 (45.5)	783 (44.5)	
Male	24 (54.5)	977 (55.5)	
WBC at diagnosis			0.83
<50,000/mL	39 (88.6)	1,521 (86.4)	
≥50,000/mL	5 (11.4)	239 (13.6)	
NCI risk			0.10
Standard risk	25 (56.8)	1,216 (69.1)	
High risk	19 (43.2)	544 (30.9)	
CNS status			0.44
CNS1, 2	43 (97.7)	1,738 (98.8)	
CNS3	1 (2.3)	22 (1.2)	
Testis involvement*			0.34
Yes	1 (4.2)	16 (1.6)	
No	23 (95.8)	961 (98.4)	
Genetic features			< 0.01
ETV6::RUNX1	4 (9.1)	309 (17.6)	
TCF3::PBX1	1 (2.3)	135 (7.7)	
KMT2A::AFF1	0 (0.0)	13 (0.7)	
Other KMT2A-r	0 (0.0)	16 (0.9)	
HHD†	3 (6.8)	461 (26.2)	
Hypodiploid‡	0 (0.0)	27 (1.5)	
Day 8 peripheral blood			1.00
Blast < 1,000 /mm³	42 (95.5)	1,670 (94.9)	
Blast ≥ 1,000 /mm³	2 (4.5)	90 (5.1)	
Day 15 BM			0.44
M1	26 (59.1)	1,205 (68.5)	
M2	12 (27.3)	382 (21.7)	
M3	5 (11.4)	164 (9.3)	
Not available	1 (2.3)	9 (0.5)	

BM, bone marrow; HHD, high-hyperdiploid.
*The proportion of patients with testis involvement was calculated based on the total number of male children (n = 24 in DS-ALL and n = 977 in Non-DS-ALL).
†HHD was defined as modal number ≥ 51
‡Hypodiploid was defined as modal number ≤ 44
§ P-values were calculated using Student's t-test for continuous variables and Fisher's exact test for categorical variables, respectively.

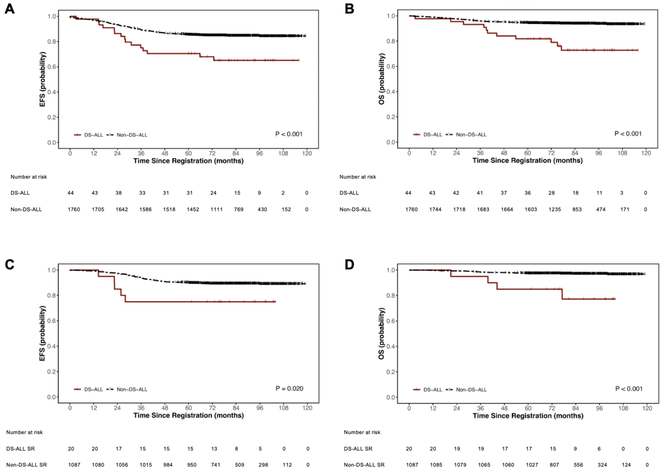

Figure 2. Survival outcomes of DS-ALL and non-DS-ALL in the ALL-B12 trial.
(A) Event-free survival (EFS) and (B) overall survival (OS) in DS-ALL versus non-DS-ALL patients. (C) EFS and (D) OS in the SR group, each comparing DS-ALL and non-DS-ALL. Among DS-ALL patients who relapsed (n = 13), isolated bone marrow events predominated (92.3%); no CNS relapse occurred.

Table 2. Multivariable Cox regression for EFS and OS

Outcome	Variable	Hazard ratio	95% CI	P value
EFS	**DS status (vs non-DS)**	**2.195**	**1.190 – 4.051**	**0.012**
	Age (per 1-year increase)	1.010	0.976 – 1.044	0.575
	Risk group (reference: SR)			
	IR	**2.443**	**1.735 – 3.440**	**< 0.001**
	HR	1.556	0.997 – 2.429	0.052
	TP2 MRD ≥ 10^{-4} (vs < 10^{-4})	**7.928**	**5.545 – 11.336**	**< 0.001**
OS	**DS status (vs non-DS)**	**3.033**	**1.386 – 6.639**	**0.006**
	Age (per 1-year increase)	1.043	0.989 – 1.101	0.121
	Risk group (reference: SR)			
	IR	**3.292**	**1.807 – 5.998**	**< 0.001**
	HR	**2.134**	**1.026 – 4.436**	**0.042**
	TP2 MRD ≥ 10^{-4} (vs < 10^{-4})	**8.839**	**5.220 – 14.967**	**< 0.001**

EFS, event-free survival; HR, high risk; IR, intermediate risk;
MRD, minimal residual disease; OS, overall survival; SR, standard risk.

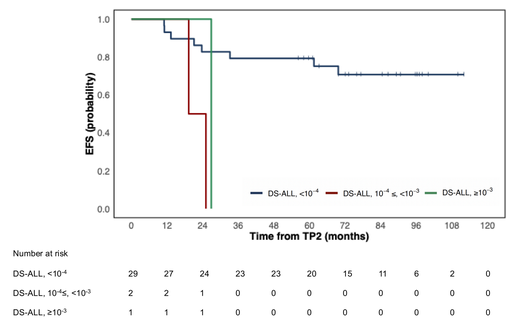

Figure 3. Event-free survival according to TP2 MRD status.
Event-free survival based on TP2 MRD category at the end of consolidation in DS-ALL. All three patients with MRD ≥10^{-4} relapsed and died within three years.

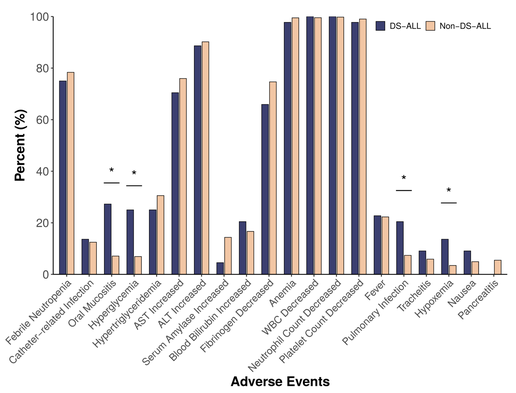

Figure 4. Comparison of treatment-related toxicities in DS-ALL and non-DS-ALL.
Overall incidence of grade 3 or higher toxicities throughout all treatment phases in DS-ALL and non-DS-ALL. Only toxicities that occurred in ≥ 5% of patients in either group are shown. Asterisks (*) indicate toxicities that were significantly more frequent in DS-ALL compared with non-DS-ALL (P < 0.05).

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