Ma-Spore ALL 2003/2010 Studies: Intensifying Rx for IKZF1 del

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On behalf of Ma-Spore ALL study group
I have no personal or financial interests to declare:
I have no financial support from an industry source at the current presentation.
Asia – 55% of world childhood cancer burden
Young population, vast landmass, LMIC
Malaysia-Singapore ALL study Group
15 year of working together

4-centre study
NMRC funding. Philanthropy
Household debt per population

Poor Asian Tigers

Source: Bank of International Settlements.
Ma-Spore: Resource limitations

Singaporean – asset rich (buy house), money poor
MediShield Life – national insurance for major illness
Co-payment – 20-40%

Malaysia
MOH – limited funding

Cost-effective care
Economic and Health outcomes of research funding
Stratified medicine

NCI Standard Risk – Age 1-10; WBC <50,000/µL
B vs T-ALL
Genetic subgroups – H>50, ETV6-RUNX1, E2A-PBX1, BCR-ABL1, MLL-AF4
Day 8 Prednisolone Response
? MLPA – IKZF1 del (P Bhatia, OP02-4)

Minimal Residual Disease quantitation
-Flow cytometry – St Jude, USA
-RQ-PCR – IgH/TCR – Ma-Spore, AIEOP-BFM, DCOG
Ma-Spore ALL 2003 study

Limited costly supportive care – open wards, Ab, Blood
Start slow – 85% 3-drug induction
PCR based MRD – 1 IgH/TCR marker only
Used MRD to decelerate therapy
Limited efficacy of high risk therapy – BMT in first CR
<table>
<thead>
<tr>
<th>Risk Group</th>
<th>MRD Risk Group</th>
<th>Ma-Spore Risk Stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard risk</td>
<td>MRD day 33 and week 12 are both ≤ 1 × 10^{-4}</td>
<td>All of the following criteria must be satisfied: MRD standard risk; CNS1 and no testicular involvement; prednisolone good response; no BCR-ABL1/MLL rearrangement/hypodiploid; Down syndrome*</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>MRD day 33 &gt; 1 × 10^{-4} and MRD week 12 &lt; 1 × 10^{-3}</td>
<td>Not Ma-Spore standard or high risk or no DNA or MRD markers</td>
</tr>
<tr>
<td>High risk</td>
<td>MRD week 12 ≥ 1 × 10^{-3}</td>
<td>Any of the following criteria satisfied: MRD high risk; prednisolone poor response; BCR-ABL1/MLL rearrangement/hypodiploid; infant CD10-negative ALL; induction failure</td>
</tr>
</tbody>
</table>
BFM ALL-IC 2002 based – except 85% has 3 drug induction
Ma-Spore ALL 2003


- **EFS**: (n = 556) 96 events; at 5 years and 6 years: 80.6% ± 3.5%
- **LFS**: (n = 556) 58 events; at 5 years and 6 years: 87.0% ± 3.3%
- **OS**: (n = 556) 57 events; at 5 years: 89.2% ± 2.7%; at 6 years: 88.4% ± 3.1%
Ma-Spore ALL 2003 – EFS by risk groups


Log-rank $P < .001$

- **Standard risk**: (n = 172) 10 events; EFS at 6 years: 93.2% ± 4.1%
- **Intermediate risk**: (n = 283) 39 events; EFS at 6 years: 83.6% ± 4.9%
- **High risk**: (n = 101) 47 events; EFS at 6 years: 51.8% ± 10%
Ma-Spore ALL 2003 – 80.6% cure

<table>
<thead>
<tr>
<th>Study</th>
<th>B-lineage†</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td>Germany BFM-05</td>
<td>79.6</td>
</tr>
<tr>
<td>USA CCG-1800</td>
<td>75</td>
</tr>
<tr>
<td>St Jude Tot-15</td>
<td>85.6</td>
</tr>
<tr>
<td>Japan TCCSG-L95</td>
<td>76.8</td>
</tr>
<tr>
<td>UKALL-97/99</td>
<td>80.0</td>
</tr>
<tr>
<td><strong>Ma-Spore 2003</strong></td>
<td><strong>80.6</strong></td>
</tr>
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</table>
3-drug induction is comparable to 4-drug
Start slow – mainly outpatient Rx

<table>
<thead>
<tr>
<th>MRD</th>
<th>Ma-Spore ALL 2003 – 3 drug</th>
<th>AIEOP-BFM 2000 – 4 drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>5-y EFS</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5y EFS</td>
</tr>
<tr>
<td>SR</td>
<td>48</td>
<td>93.2</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>92.3</td>
</tr>
<tr>
<td>IR</td>
<td>45</td>
<td>83.5</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>77.6</td>
</tr>
<tr>
<td>HR</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>50.1</td>
</tr>
</tbody>
</table>
Alteration in B-cell development genes -> ALL

Mullighan et al. Leukemia
**IKZF1** del confers adverse outcome in B-LL including BCR-ABL1+

Clappier et al. Leukemia 2015;29: 2154

Van der Veer A et al. Blood. 2014;123:1691
Vincristine-dexa pulse on IKZF1del - conflicting

Clappier et al. Leukemia 2015;29: 2154
Hinze et al. BFM 95. Leukemia 2017
Ma-Spore ALL 2010: **Intensifying Rx for** $IKZF1^{\text{del}}$

- **Prospective study**
- **Upgraded patients with** $IKZF1^{\text{del}}$ **to the next higher risk group**
  - SR upgraded to IR and
  - IR upgraded to HR (had 2 blocks of FLADnr)
  - BCR-ABL1+ - added continuous imatinib from D15 to end maintenance therapy

and compared corresponding outcome in Ma-Spore ALL 2003.
823 children with B-Lymphoblastic Leukaemia

MLPA

No DNA/results n = 138

Ma-Spore ALL 2003 n=410
- IKZF1$^{\text{del}}$  n = 59
- Defaulted  n =19

Outcome analysis n = 391
- IKZF1$^{\text{del}}$  n = 56 (14.4%)
- IKZF1 wt  n = 335

Ma-Spore ALL 2010 n=275
- IKZF1$^{\text{del}}$  n = 50
- Defaulted  n = 6

Outcome analysis n = 268
- IKZF1$^{\text{del}}$  n = 50 (18.2%)
- IKZF1 wt  n = 218
## Stratification in Ma-Spore (MS) studies

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<tr>
<th>Risk Group</th>
<th>MS2003*</th>
<th>MS2010**</th>
</tr>
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<tbody>
<tr>
<td><strong>SR</strong> (all criteria)</td>
<td>MRD$\leq 1 \times 10^{-4}$ at Week 5 &amp; 12 CNS 1/No testicular involvement</td>
<td>MRD$\leq 1 \times 10^{-4}$ at Week 5, 8, 12 No $IKZF1_{\text{del}}$ Age$&lt;10$</td>
</tr>
<tr>
<td><strong>IR</strong></td>
<td>Others No MRD data (no material or insensitive marker)</td>
<td>MRD negative with $IKZF1_{\text{del}}$</td>
</tr>
<tr>
<td><strong>HR</strong> (any criterion fulfilled)</td>
<td>MRD$\geq 1 \times 10^{-3}$ at Week 12 Prednisolone poor response Day 8 $BCR-ABL1$, $MLL-r$, or hypodip (&lt;45 chr) Induction failure</td>
<td>MRD$\geq 1 \times 10^{-2}$ at Week 5 or MRD$\geq 1 \times 10^{-3}$ at Week 8 or MRD$\geq 1 \times 10^{-4}$ at Week 12 or MRD positive with $IKZF1_{\text{del}}$</td>
</tr>
</tbody>
</table>

*Yeoh AEJ et al. J Clin Oncol 2012  
** Yeoh AEJ et al. J Clin Oncol 2018
Intensifying Treatment of Childhood B-Lymphoblastic Leukemia With IKZF1 Deletion Reduces Relapse and Improves Overall Survival: Results of Malaysia-Singapore ALL 2010 Study

Allen Eng Juh Yeoh, Yi Lu, Winnie Hui Ni Chin, Edwynn Kean Hui Chiew, Evelyn Huizi Lim, Zhenhua Li, Shirley Kow Yin Kham, Yiong Huak Chan, Wan Ariffin Abdullah, Hai Peng Lin, Lee Lee Chan, Joyce Ching Mei Lam, Poh Lin Tan, Thuan Chong Quah, Ah Moy Tan, and Hany Ariffin

J Clin Oncol. 2018 Sep 10;36(26):2726-2735
MS2003 vs MS2010 - *IKZF1* deletions

Relapse reduced significantly from 30.4% to 13.5% (p=.05)

Overall Survival improves from 69.6% vs 91.6% (p=.007)
Intervening by intensification Ikaros deletion (Ma-Spore ALL 2003 vs 2010)

**IKZF1 (P<0.001)**

- N=46, 0.33 (0.20‒0.46)
- N=289, 0.11 (0.07‒0.14)

**IKZF1 (P=0.178)**

- N=35, 0.17 (0.05‒0.35)
- N=162, 0.09 (0.04‒0.16)
Ma-Spore ALL 2003 (MS2003) vs Ma-Spore ALL 2010 (MS2010)
Remarkable Improvement in Survival of HIGH-RISK Childhood ALL from 66.3% to 83.6% (p=0.000)

MS10 5-yr OS 83.6% (N=84)
MS10 5-yr EFS 65.6% (N=84)
MS03 5-yr OS 66.3% (N=120)
MS03 5-yr EFS 48.1% (N=120)
P=0.000
Replication Fork

http://kvhs.nbed.nb.ca/gallant/biology/replication_overview.jpg  Fig. 16.16
Guanine pairs with cytosine – 3 hydrogen bonds
Gertrude Elion – Nobel Prize 1988

6-Mercaptopurine
Mercaptopurine – designed analog to block pairing
Stuck Zipper – fail DNA replication
East Asian Ancestry has Lower 6MP Tolerance
NUDT15 variants

*1

- c36_37insGGAGTC

*2

- p.V18_V19insGV
- C415T

*3

- p.R139C
- C415T

*4

- p.R139C
- G416A

*5

- p.V18I
- G52A

*6

- p.V18_V19insGV
- c36_37insGGAGTC
NUDT15 and TPMT wild type: Genetic score 0
R740 BMGZX_Maintenance Phase Normalized 6MP dosage (mg/m²/day)

No. of Days

Weeks

Normalized 6MP dosage (mg/m²/day)

NUDT15 415TT
Combining NUDT15 and TPMT variants
Genetic score – 1 in 50 very sensitive to MP

Ma-Spore ALL 2003 (n=485)

Score 0, 77.5%
Score 1, 20.5%
Score 2, 2.0%
ASEAN+ TGN study: Ma-Spore, Vietnam, Philippines, Myanmar, Pakistan, India

NMRC funded. Collaboration with Yang Jun, SJCRH.

NUH + VNCH  → ASEAN+ TGN study

NUH, KKH
UMMC
PGH, SPMC
VNCH, Hue
Yangon
Aga Khan U
Fortis India
NUDT15 – many destructive variants

1) NUDT15 diplotype inference
   - Ambiguity of diplotype in cases heterozygous for ins36_37 and C415T
Immune-Based Therapies in Newly Diagnosed ALL Era of Ultra-expensive therapy

- **Blinatumomab**
  - US$175,000 per year

- **Inotuzumab**
  - US$168,300 per course

- **Chimeric antigen receptor (CAR) T-cells CD19/22**
  - US$475,000
  - Bespoke, made for each patient.
  - Scaling, expensive cGMP
CD19 – highly expressed; CD 22 – lower density

Cytokine Release Syndrome – immune therapy
Cytokine Release Encephalopathy Syndrome
B-cell aplasia – monthly IGIV
HBV+, HCV+, HIV → viral reactivation
Tuberculosis
Cardiac damage
Long term ??? – pregnancy – fetal B-aplasia
Ma–Spore ALL 2010 AYA vs HyperCVAD

Pediatric-Inspired Protocol Improved Overall Survival in Young Adult Aged 18-30 Years old with Philadelphia-Negative ALL Compared to the Standard Adult Hypercvad Protocol

VLT Ling WT, E Seah, M Poon, M Ooi, AEJ Yeoh and CH Ng
Blood 2017 130:5043. ASH 2017

MaSpore 2010 84% 76%
HyperCVAD 46% 39%

MaSpore n=16
CVAD n=14

Leukemia Free Survival

MaSpore n=16
CVAD n=14
Ma-Spore ALL 2003/2010 studies
Malaysia catching up – limits of chemoRx

**Malaysia: UMMC**

- **MS10 5y EFS 87.4% (N=174)**
- **MS03 5y EFS 75.2% (N=344)**
- **UHALL95 5y EFS 55% (N=339)**

**NUH**

- **MS10 5yrs EFS 90% (N=86)**
- **MS03 5yrs EFS 87.5% (N=89)**
- **HK-SG 5yrs EFS 79% (N=40)**
RNASeq – precision medicine for ALL
- So many drivers of ALL

Pui et al. J Clin Oncol
Ma-Spore ALL 2020

Better risk stratification
RNA-Seq to subtype ALL
NGS MRD to measure response

Limits of chemotherapy and BMT
Immune and Cell Therapy
IV rituximab in delayed intensification for CD 20+ SR/IR
Rituximab is affordable

CAR-T CD19 in high risk B-lineage ALL (cost-effectiveness, QoL)
-ALaCART 19 study
Acute Leukaemia and Chimeric Antigen Receptor in T-cell for CD19
-5 children, 1 young adult Rx on compassionate
Personalised Medicine

**Current**

- Morphology + cytochemistry
- Flow cytometry
  - B vs T
- Cytogenetics
  - Hyperdiploid > 50
  - Hypodiploid < 44
- OFT
  - BCR-ABL1
  - MLL-AF4
  - E2A-PBX1
  - ETV6-RUNX1

**Future**

- Real-time PCR
- MRD
- Multiparametric flow
  - Flow MRD
- Pharmacogenomics
  - TPMT, NUDT15
- Microarray GEP
- Next generation sequencing
  - RNA seq
  - Exome profiling
  - Whole genome seq
Ma-Spore ALL study
Made possible because of many: